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Editors

JEAN D. WILSON, M.D.
Professor of Internal Medicine, The University of Texas
Southwestern Medical Center, Dallas

EUGENE BRAUNWALD, A.B., M.D.,
M.A. (Hon.), M.D. (Hon.)
Harvey Professor of the Theory and Practice of Physic,
Harvard Medical School; Chairman, Department of
Medicine, Brigham and Women's Hospital, Boston

KURT J. ISSELBACHER, A.B., M.D.
Mallinckrodt Professor of Medicine, Harvard Medical
School; Director, Cancer Center, Massachusetts Gen-
eral Hospital, Boston

ROBERT G. PETERSDORF, A.B., M.D.,
M.A. (Hon.), D.Sc. (Hon.), M.D. (Hon.), L.H.D. (Hon.)
President, Association of American Medical Colleges,
Washington, D.C.

JOSEPH B. MARTIN, M.D., Ph.D.,
F.R.C.P. (C), M.A. (Hon.)
Professor of Neurology and Dean, School of Medicine,
University of California at San Francisco, San Francisco

ANTHONY S. FAUCI, M.D.
Director, National Institute of Allergy and Infectious
Diseases; Chief, Laboratory of Immunoregulation; Di-
rector, Office of AIDS Research, National Institutes of
Health, Bethesda

RICHARD K. ROOT, M.D.
Professor of Medicine and Associate Dean for Clinical
Education, School of Medicine, University of California
at San Francisco, San Francisco

HARRISON'S

PRINCIPLES OF INTERNAL MEDICINE

TWELFTH EDITION

COMPANION HANDBOOK

Editors

JEAN D. WILSON

EUGENE BRAUNWALD

KURT J. ISSELBACHER

ROBERT G. PETERSDORF

JOSEPH B. MARTIN

ANTHONY S. FAUCI

RICHARD K. ROOT

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predict morbidity and mortality is determined solely by nutritional status.

- ARJANA NS, ROCHSTER DF: Effect of body weight and muscularity on human diaphragm muscle mass, thickness and area. *J Appl Physiol* 52:64, 1982
- BARACOS V et al: Regulation of degradation of muscle proteins during fever: A mechanism for the increased degradation of muscle proteins during fever. *N Engl J Med* 308:553, 1983
- BECKER DJ: The endocrine responses to protein calorie malnutrition. *Ann Rev Nutr* 3:147, 1983
- BECKER B, CERAMI A: Cachectin: More than a tumor necrosis factor. *N Engl J Med* 316:379, 1987
- BISHMAN RR et al: Protein status of general surgical patients. *JAMA* 230:858, 1974
- BISHMAN RR et al: Prevalence of malnutrition in general medical patients. *JAMA* 235:1567, 1976
- CAGILL GF: Starvation in man. *N Engl J Med* 282:668, 1970
- D'ARIELLO CA: Interleukin 1. *Rev Infect Dis* 6:53, 1984
- HEYMFIELD SB, WILLIAMS PJ: Nutritional assessment by clinical and biochemical methods. In *Modern Nutrition in Health and Disease*, 7th ed, ME Shils, VR Young (eds). Philadelphia, Lea & Febiger, 1988
- HEYMFIELD SB et al: Cardiac abnormalities in cachectic patients before and during nutritional repletion. *Am Heart J* 95:584, 1978
- KRECH G, FARHING MG: Nutrition and infection. *Ann Rev Nutr* 6:131, 1986
- ROSENBLATT S et al: Exchange of amino acids by muscle and liver in sepsis. *Arch Surg* 118:167, 1983
- TEN-STATE NUTRITION SURVEY, 1968-70. US Department of Health, Education, and Welfare Publication (HSM) 73, 1972
- WELSHER RL et al: A prospective evaluation of general medical patients during the course of hospitalization. *Am J Clin Nutr* 32:418, 1979
- WORLD HEALTH ORGANIZATION: *Infants and Young Child Nutrition*. Report by the Director General to the World Health Assembly. Document WHA 36/1983/70, March, 1983

72 OBESITY

JERROLD M. OLEFSKY

The ability to store food energy as fat provides survival value when the food supply is scarce or sporadic. Unlike glycogen or protein, triglyceride does not require water or electrolytes for storage purposes and can be retained essentially as pure fat; 1 g adipose tissue yields close to the full theoretical equivalent of 38 kJ (9 kcal). Because of the efficient storage of energy in adipose tissue, an individual of normal weight can survive up to 2 months of total starvation. However, western society is generally not characterized by periodic or insufficient food supply but rather by constant and abundant food. As a consequence, the ability to store fat all too frequently is of negative survival value because of overconsumption and the resulting obesity.

DEFINITION AND INCIDENCE Obesity can most easily be assessed in terms of height and weight. One way is to relate weight to an average range for height and age. This measure of *relative weight* can lead to an underestimation of the incidence of obesity, since in the United States the "average" individual is somewhat obese. Tables of *ideal and desirable weight* are based on actuarial estimates of what is consistent with longest life expectancy. Such tables are more useful if adjusted for differences in body build. An alternative method of estimating obesity is the *body mass index* or *BMI* [body weight (in kilograms) divided by height (in meters)²]. For adults ages 20 to 29, the 85th percentile for BMI is 27.8 for males and 27.3 for females. Although relative weight and BMI correlate with the degree of adiposity, excess poundage can be either lean or fat tissue. For example, heavily muscled individuals would be considered obese using these measurements. Nevertheless, such assessments correlate fairly well with the risk of adverse effects on health and longevity. More precise assessment of obesity can be made with measurements of body density or with isotopic dilution methods, but these are unsuitable for routine use. Alternatively anthropometry can be utilized

for assessing the degree of adiposity. Assessment of skin-fold thickness over various areas of the body together with height, weight, and age can be used to assess the degree of adiposity. Triceps and subscapular skin folds are most commonly employed (see Chap. 71). From a health standpoint, certain patterns of obesity may be less desirable than others. Fat deposition about the waist and flank, as evidenced by a high ratio of waist to hip circumference, is associated with a greater health risk than fat deposition at the hips.

The term *obesity* implies an excess of adipose tissue, but the meaning of excess is hard to define. Aesthetic considerations aside, obesity can best be viewed as any degree of excess adiposity that imparts a health risk. This cutoff between normal and obese can only be approximated, and the health risk imparted by obesity is probably a continuum with increasing adiposity. The Framingham Study demonstrated that a 20 percent excess over desirable weight clearly imparted a health risk. A National Institutes of Health consensus panel on obesity agreed with this definition and concluded that a 20 percent increase in relative weight or a BMI above the 85th percentile for young adults constitutes a health risk; by use of these criteria 20 to 30 percent of adult men and 30 to 40 percent of adult women are obese, with the highest rates among the poor and minority groups. Significant health risks at lower levels of obesity can occur in the presence of diabetes, hypertension, heart disease, or other associated risk factors.

The Surgeon General's 1988 Report on obesity notes that even mild obesity increases the risk for premature death, diabetes, hypertension, atherosclerosis, gallbladder disease, and certain types of cancer. In the United States the prevalence of obesity has increased in the past few decades. Because of the high prevalence of obesity and its health consequences, its prevention and treatment should be a high public health priority.

ETIOLOGY When energy intake exceeds expenditure, the excess calories are stored in adipose tissue, and if this net positive balance is prolonged, obesity results, i.e., there are two components to weight balance, and an abnormality on either side (intake or expenditure) can lead to obesity.

The regulation of eating behavior is incompletely understood. To some extent, appetite is controlled by discrete areas in the hypothalamus: a feeding center in the ventrolateral nucleus of the hypothalamus (VLH) and a satiety center in the ventromedial hypothalamus (VMH). The cerebral cortex receives positive signals from the feeding center that stimulate eating (Fig. 72-1), and the satiety center modulates this process by sending inhibitory impulses to the feeding center. In animals destruction of the feeding center results in decreased food intake, and destruction of the satiety center leads to overeating and obesity. Several regulatory processes may influence these hypothalamic centers. The satiety center may be activated by the increases in plasma glucose and/or insulin that follow a meal. It is of interest in this regard that the VMH contains insulin receptors and is insulin-sensitive. Meal-induced gastric distention is another possible inhibitory factor. The total adipose tissue mass may also influence the activity of the hypothalamic centers; i.e., there is a relatively fixed "set point" for body adiposity. An elevated set point may account for the frequent recidivism in obese patients who have lost weight. How the "set point" is established and how the hypothalamus senses total fat stores are unknown. Glycerol release from fat cells, ascending neural impulses, and/or circulation of adipocyte-derived peptides such as adiponin may be signals of adipose tissue size. Additionally, the hypothalamic centers are sensitive to catecholamines, and beta-adrenergic stimulation inhibits eating behavior. This provides at least one rationale for the anorexic effects of amphetamines.

Ultimately, the cerebral cortex controls eating behavior, and impulses from the feeding center to the cerebral cortex are only one input. Psychological, social, and genetic factors also influence food intake. In many obese subjects these influences are overriding; indeed, obese subjects usually respond to external signals such as time of day, social setting, and smell or taste of food to a greater extent than do persons of normal weight.

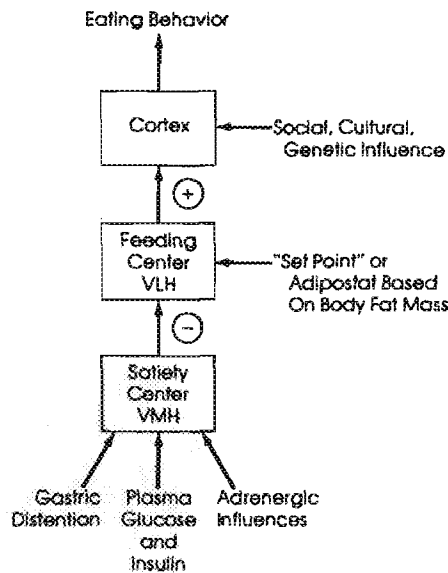


FIGURE 72-1 The regulation of eating. The ventromedial satiety center is considered to be inhibitory, and the ventrolateral feeding center stimulatory. See text for discussion.

Although overeating is the usual cause of obesity, other factors may participate. Daily caloric needs normally range between 110 to 130 kJ (27 to 32 kcal) per kilogram of body weight; this figure is higher in active and lower in sedentary individuals. Physical activity clearly modulates overall caloric balance, and obese individuals tend to be less active. This can be a contributory factor in the maintenance of excess weight, but decreased physical activity is unlikely to be an important cause of major weight gain in most obese subjects. Rather, obesity leads to inactivity. The modest increase in weight that often accompanies the middle years may be related more directly to diminished physical activity. Injury or illness may lead to chronic restricted activity and predispose to weight gain unless caloric intake is appropriately curtailed. Perhaps the greatest factor tending to diminish the output side of the equation is simply a sedentary lifestyle.

Decreased caloric expenditure and a metabolic abnormality associated with overefficient caloric utilization have also been postulated as involved in the pathogenesis of obesity. With rare exceptions major metabolic abnormalities have not been detected in obese individuals, although subtle defects may be undetected. There are three major components to overall energy expenditure: resting metabolic rate, exercise-induced thermogenesis, and the thermic response to food.

The resting metabolic rate accounts for 60 to 75 percent of daily energy expenditure and is measured in a thermoneutral environment while the subject is at rest following an overnight fast and several hours after any significant physical activity. An average resting metabolic rate in a 70-kg man is 6300 kJ (1500 kcal)/d. The resting metabolic rate should be expressed as a function of fat-free body weight (by subtracting the subject's total adipose mass from body weight), since triglyceride mass is metabolically inert in that negligible energy is expended to maintain triglyceride depots. When expressed in this way, the resting metabolic rate is normal in most obese subjects. However, a distinction must be made between static obesity and the actual process of gaining weight. When normal subjects consume hypercaloric diets, less weight is gained than would be predicted on the basis of the excess calories ingested. This effect is most marked when carbohydrate is consumed and disappears when the excess calories consist of fat. Thus, humans can apparently partially adapt to chronic excessive carbohydrate and protein intake,

and this protective effect attenuates the weight gain. Part of this adaptive response is related to an increase in thermogenesis manifested as an increase in the resting metabolic rate. The mechanism of adaptive thermogenesis is unknown, but overeating of carbohydrate or mixed nutrients leads to increased plasma levels of triiodothyronine (T_3) and decreased levels of reverse T_3 (rT_3). A converse effect is seen in starvation with decreased T_3 and increased rT_3 levels. The conversion of thyroxine to T_3 occurs largely in the liver; excess food may induce adaptive thermogenesis by increasing the concentration of T_3 relative to that of T_4 and rT_3 . Increased central or peripheral sympathetic outflow leading to increased catecholamine-induced caloric utilization and increased heat production may also play a role in the thermogenic response to overnutrition. Adaptive thermogenesis can lead to a 10- to 15-percent increase in resting metabolic rate, and this effect is seen after a 2- to 3-week period of hypercaloric intake. The rate of onset and the degree of adaptive thermogenesis is the same in obese and nonobese individuals when expressed on the basis of fat-free body mass. Specifically, the increase in resting metabolic rate, changes in thyroid hormone metabolism, and thermic responses to infused catecholamines are similar in normal and obese subjects during periods of overnutrition.

Work performance, or energy expenditure per standard physical work load, can be normal or increased in obesity depending on the kind of work performed. The energy expenditure of exercise is increased in obese compared to lean subjects due to the extra effort involved in moving or supporting an increased body mass. When this effect of increased body mass is taken into account, work performance is normal in obesity. Clearly, normal or increased energy expenditure during physical work cannot contribute to the development of obesity. On the other hand, the total daily energy expenditure due to exercise is less in many sedentary obese subjects simply because they engage in less daily physical activity than their lean counterparts.

The third important aspect of caloric balance is the thermic response to food, so-called dietary thermogenesis. This consists of the heat, or energy, expended above the resting metabolic rate for several hours after the ingestion of a meal. About 75 percent of the thermic response to food is due to the energy cost of digestion, absorption, metabolism, and storage of foodstuffs; the remainder is probably due to activation of the sympathetic nervous system. The heat produced following nutrient ingestion is a form of caloric expenditure and is greater for protein and less for carbohydrate and fat. The thermic response to mixed meals can equal 10 to 15 percent of the calories ingested, and decreased thermic responses have been described in some studies of human obesity. This difference may be due to altered flux rates through different pathways of intermediary metabolism, with more energy-efficient pathways being favored in obesity. As an example, the higher the rate of glucose utilization, the greater the thermic response to carbohydrate-containing meals, and small decreases in the thermic response to food may be due to insulin resistance and decreased glucose disposal in obese subjects. It is clear that small differences in caloric utilization maintained over years can lead to a significant net positive caloric balance. However, while it is tempting to postulate that this decreased thermic response may contribute to obesity, most of the published comparisons have been made between normal persons and subjects who are already obese. Thus, the obesity-associated changes in thermic response to food may be secondary to the obese state rather than a primary abnormality. More importantly, differences in the thermic response to meals between the obese and nonobese are at most in the range of 125 to 210 kJ (30 to 50 kcal)/d. Such minor differences can easily be counterbalanced by minor decreases in food intake and/or increases in exercise-induced thermogenesis. Since such compensation does not occur, it seems more probable that obesity is the result of impaired coupling between caloric intake and expenditure.

Another potential regulatory process in the control of adipose tissue mass involves adipose tissue lipoprotein lipase (ATLPL). This enzyme is synthesized within adipocytes, secreted into the extracellular space, and attached to the luminal surface of nearby endothelial cells.

At this location ATLPL hydrolyzes fatty acids from the triglycerides of circulating triglyceride-rich lipoproteins. The released fatty acids are taken up by adipocytes, converted to triglycerides, and stored. Thus, ATLPL participates in the storage of excess fat calories in adipose tissue. The *lipoprotein lipase hypothesis* holds that in some obese states excessive levels of this enzyme induce obesity by causing preferential deposition of fat calories in adipose tissue. In support of this hypothesis, ATLPL levels are increased in obese rodents and humans. More importantly, levels of this enzyme do not return to normal following weight reduction. This latter finding is of particular interest since it is one of the few characteristics of the obese state that is not corrected by weight reduction and could explain the propensity of obese patients to regain lost weight.

Environmental, cultural, and genetic influences all contribute to obesity, and in population studies it is impossible to quantitate the separate impact of these factors. Nevertheless, the importance of genetics has been demonstrated in studies of twins and adopted siblings. The BMI of adopted individuals correlates better with that of the biologic rather than the adoptive parents. Among biologic and adoptive siblings, the amount and distribution of fat is associated with a genetic relationship, and similarities are not as close among adopted siblings. Most likely, both nature and nurture contribute to the etiology of obesity.

SECONDARY OBESITY Hypothyroidism Obesity can result from hypothyroidism because of decreased caloric needs. However, only a minority of hypothyroid patients are truly obese, and an even smaller proportion of obese patients are hypothyroid. Indiscriminate use of thyroid hormone in the treatment of obesity is to be deplored and should never be instituted in the absence of documentation of decreased thyroid function.

Cushing's disease Cushing's disease is a rare cause of obesity. Hyperadrenocorticism elicits a typical pattern of obesity with predominantly centripetal fat stores, characteristic rounded or moon facies, and cervical or supraclavicular fat deposits.

Insulinoma Hyperinsulinemia, secondary to an insulinoma, can occasionally cause obesity, presumably because of increased caloric intake secondary to recurrent hypoglycemia. Most patients with islet cell tumors and hypoglycemia are not obese.

Hypothalamic disorders Froehlich's syndrome in boys is characterized by obesity and hypogonadotrophic hypogonadism with other variable features such as diabetes insipidus, visual impairment, and mental retardation. The anterior pituitary is usually normal, and the syndrome is thought to be the result of hypothalamic dysfunction. This syndrome likely includes a number of overlapping disorders having in common a hypothalamic lesion that leads to overeating and to hypogonadotrophism. Occasionally pituitary tumors are present (as in Froehlich's original case) that may physically impair the hypothalamus.

Other rare causes of obesity include the Laurence-Moon-Biedl syndrome, characterized by retinitis pigmentosa, mental retardation, skull deformities, polydactyly and syndactyly, and the Prader-Willi syndrome, which is associated with hypotonia, mental retardation, and a predilection for diabetes mellitus. Both of these disorders also feature obesity and hypogonadism that are thought to be hypothalamic in origin.

PATHOLOGIC SEQUELAE Increased adipose tissue stores are deposited subcutaneously, around all internal organs, throughout the omentum, and in the intramuscular spaces. Obese individuals also have an expansion of lean body mass as evidenced by increased size of the kidneys, heart, liver, and skeletal muscle mass. Fatty livers are common in extreme obesity.

Adipocyte size and number Attempts have been made to classify obese individuals on the basis of the relative degree of adipocyte hypertrophy versus hyperplasia. This classification scheme was generated as the result of experimental data indicating that in several rodent species and in humans the capacity to increase adipocyte number exists for only a limited period in early life and perhaps at the time of puberty. Thus, prior to reaching adulthood the ability to

increase the number of adipocytes declines, and after this time expansion of adipose tissue mass is accompanied primarily by an increase in fat-cell size. Individuals with severe obesity have both increased adipocyte size and number, and those with the greatest degree of adipocyte hyperplasia have a strong tendency toward onset of obesity early in life. Patients having mild to moderate obesity show predominantly adipocyte hypertrophy, and the onset is usually during adult life. Weight reduction leads to a decrease in adipocyte size with no change in cell number. The above observations led to the concept of the existence of a "critical period" in early life when final adipocyte number is determined and after which cell number cannot be changed. This formulation implies that alterations in adipocyte number can only be induced during this critical period. However, the concept of a strictly defined critical period for hyperplasia of the adipocytes is only partially correct. When severe obesity is induced in adult rats, both adipocyte number and cell size increase. Adipocyte hypercellularity also occurs in some patients with adult-onset obesity.

Thus while substantial overnutrition at any stage of life can lead to hypertrophy of individual existing adipocytes, there are periods during childhood and adolescence when overnutrition has an enhanced ability to induce the development of new adipocytes. Furthermore, even in adult life, if the degree of overnutrition is sufficient to induce existing adipocytes to enlarge to some limiting size, then new adipocytes will form. Whether this latter population of cells represents new cell formation or simply the filling with lipid of previously undetectable preadipocytes formed earlier in life is not known. Regardless of the cause or time of development of increased adiposity (adipocyte hypertrophy with or without hyperplasia), subsequent weight reduction only leads to a decrease in the size of existing adipocytes and not a decrease in adipocyte number. Thus, once a given complement of adipocytes is attained, this number is fixed and cannot be reduced.

METABOLIC SEQUELAE Obesity has a profound impact on diabetes mellitus and on various hyperlipoproteinemic states primarily through its influences on insulin secretion and insulin sensitivity.

Hyperinsulinemia: insulin resistance Increased insulin secretion is a common feature of obesity. It occurs in the basal state and in response to a wide variety of insulinogenic agents. A correlation exists between the degree of obesity and the magnitude of the hyperinsulinemia—particularly the basal insulin levels. Some obese patients exhibit hyperglycemia or frank diabetes in the face of hyperinsulinemia. The combination of hyper- or euglycemia and hyperinsulinemia indicates an insulin-resistant state, and decreased hypoglycemic responses to insulin are common in obese humans and animals. Insulin resistance could be due to an abnormal beta-cell product, circulating insulin antagonists, or tissue insulin insensitivity. Since abnormal islet secretory products or circulating antagonists have not been identified, it is thought that the insulin resistance of obesity is primarily due to tissue insensitivity. The initial step in the cellular action of insulin involves binding to cell surface receptors in target tissues. Cells from obese animals and humans contain decreased numbers of insulin receptors, and this decrease doubtless plays a role in the insulin resistance. However, other factors participate. The enlarged adipocytes of obese rats have both a decrease in insulin receptors and an even greater defect in the capacity to metabolize glucose, suggesting a major biochemical abnormality distal to the receptor mechanism. A similar postreceptor defect presumably exists in other insulin target tissues such as muscle and liver. In the obese human insulin resistance is due to a combination of receptor and postreceptor defects in insulin action. In those obese patients with the mildest degree of hyperinsulinemia and insulin resistance, the decrease in insulin action is predominantly due to a decreased number of insulin receptors. As the insulin-resistant state worsens, a postreceptor defect emerges, and in obese subjects with the most severe degree of insulin resistance, the postreceptor defect is the predominant abnormality.

Diabetes mellitus (See also Chap. 319) Although only a minority of obese patients are diabetic, the converse is not the case. Non-insulin-dependent, or type II, diabetes comprises about 90 percent of the diabetic population in the United States, and 80 to 90 percent of type II diabetics are obese. Obesity is an important contributory factor to the diabetes in these patients, predominantly through its influences on insulin resistance. Obesity exacerbates the diabetic state, and in many cases diabetes can be ameliorated by weight reduction.

Hyperlipoproteinemia (See also Chap. 326) Most plasma cholesterol circulates in the low-density lipoprotein (LDL) fraction, and, in the fasting state, very low density lipoproteins (VLDL) contain most of the circulating triglyceride. The association between obesity and elevated LDL levels is modest at best, especially when the relationship is corrected for factors such as age. Total-body cholesterol is increased in obesity, but this is mainly accounted for by adipose tissue cholesterol stores. Cholesterol turnover may be increased, leading to increased biliary excretion of cholesterol. This may contribute to the increased incidence of gallstone formation. Obesity has a more pronounced effect on VLDL metabolism. Hypertriglyceridemia is frequent, and the degree of obesity correlates with the level of hypertriglyceridemia. The increased triglyceride levels are due to increased hepatic VLDL production with no defect in the removal of VLDL from plasma. As discussed above, plasma insulin levels are elevated, particularly in the portal venous blood. Hyperinsulinemia can promote increased hepatic VLDL synthesis and secretion. In addition, increased plasma free fatty acid (FFA) turnover exists in obesity, and FFA extraction by the liver provides an important precursor for hepatic triglyceride synthesis. Thus, the hypertriglyceridemia in obesity may be secondary to increased hepatic VLDL secretion due to hyperinsulinemia and augmented FFA availability.

MANIFESTATIONS AND COMPLICATIONS Gross obesity produces mechanical and physical stresses that aggravate or cause a number of disorders including osteoarthritis (especially of the hips) and sciatica. Varicose veins, thromboembolism, ventral and hiatal hernias, and cholelithiasis are also more common.

Hypertension In significantly obese persons, use of the standard size blood pressure cuff leads to erroneously high readings; an oversize cuff should always be used. A strong association between hypertension and obesity is observed even when accurate measurements are obtained. The mechanism by which obesity causes hypertension is uncertain, but peripheral vascular resistance is usually normal while blood volume is increased. Weight loss leads to reductions in systemic blood pressure independent of changes in sodium balance.

Hypoventilation syndrome (Pickwickian syndrome) The obesity-hypoventilation syndrome is a heterogeneous group of disorders with differing clinical manifestations. The hypersomnolence that can occur in obesity is a manifestation of nighttime sleep apnea. In these individuals, once sleep begins, upper airway obstruction leads to hypoxemia and hypercapnia, causing arousal with return of normal respiration. Many such episodes occur each night, leading to chronic sleep deprivation and daytime somnolence. The combination of the obese habitus plus sleep-induced relaxation of the pharyngeal musculature is believed to be the cause of the intermittent upper airway obstruction. Occasionally such episodes are life-threatening (causing serious cardiac arrhythmias) and require long-term tracheostomy therapy. Chronic daytime hypoventilation is usually not as severe as that occurring during sleep and may be due to abnormalities of the respiratory control centers. Patients with hypoventilation display blunted ventilatory responses to hypercapnia and hypoxia and often develop hypercapnia and hypoxemia due to decreased basal ventilation; in addition, ventilation-perfusion mismatch may result from mechanical factors. In severe cases polycythemia, pulmonary hypertension, and cor pulmonale can result. Weight reduction will reverse these abnormalities if instituted before permanent cardiac damage develops. Some obese patients with sleep apnea and hypersomnolence

do not have daytime hypoventilation and have normal ventilatory responses to hypoxia and hypercapnia. Progestational agents have been used therapeutically in the obesity-hypoventilation syndrome since they stimulate the ventilatory response to hypercapnia and hypoxia in normal subjects. Medroxyprogesterone increases ventilation and improves heart failure and erythrocytosis in these patients, although obstructive sleep apnea continues.

Adrenal function Although Cushing's disease can usually be distinguished from simple obesity on clinical grounds, laboratory testing is occasionally necessary. This can lead to confusion since 24-h urinary 17-hydroxycorticoid excretion is often elevated in obesity. Less commonly, plasma cortisol levels are also increased. Corticosteroid levels are usually suppressible with dexamethasone in obesity, but occasionally suppression is incomplete, rendering the diagnosis difficult (also see Chap. 317).

Growth hormone Secretory responses of growth hormone to a variety of stimuli such as hypoglycemia, exercise, and arginine infusion are reduced, and the starvation-induced rise in plasma growth hormone levels is attenuated.

Atherosclerosis Obesity is a risk factor for the development of coronary artery disease and stroke. Most of the risk is mediated through the associated hypertension, hyperlipoproteinemia, and diabetes. Nevertheless, even when these abnormalities are factored out, an additional, smaller risk can be ascribed to obesity per se.

TREATMENT Amelioration of hyperinsulinemia, insulin resistance, diabetes, hypertension, and hyperlipidemia can occur following weight loss. These changes are significant and enduring provided the weight loss is maintained. During weight loss all adipose tissue depots diminish proportionately. Sometimes generalized loss does not produce the attractive cosmetic effects desired. Many techniques have been proposed to effect selective adipose tissue reduction over particular regions of the body, but none is effective.

Methods of weight reduction In instances where obesity is secondary, the appropriate therapy is to treat the underlying disease. Most of the time the difficult problem of primary weight reduction must be undertaken.

Diet Caloric restriction is the cornerstone of weight reduction. From the standpoint of patient and physician this is a frustrating and demanding undertaking. The basic principles are simple. If food intake is less than energy expenditure, stored calories, predominantly in the form of fat, will be consumed. In general, a deficit of 32,000 kJ (7700 kcal) leads to loss of about 1 kg fat. By estimating the patient's daily caloric needs [approximately 125 to 150 kJ (30 to 35 kcal) per kilogram of body weight], one can calculate the daily deficit necessary to achieve a given rate of weight loss.

Dietary restriction can range from total starvation to mild caloric deprivation, and these approaches will be discussed separately. Dietary recommendations are most effective when they are specific and geared to the patient's life-style. A dietician or a similarly trained health professional should interview each patient and estimate average daily caloric intake, identify food preferences, and characterize the eating patterns. The amount of calories to be consumed on the restricted diet should be carefully explained in terms of quantities of specific foodstuffs. Frequently, the therapist must balance the degree of restriction against potential noncompliance. The more restrictive the diet, the more rapid the weight loss, but this often leads to a greater rate of nonadherence. It is preferable to design a diet with which the patient is comfortable and that produces a modest but steady weight loss.

Schemes for weight reduction have become a profitable business in the United States, and there are almost as many diets as there are therapists. Each proponent claims that the presence or absence of certain foodstuffs is desirable for more effective weight loss. However, little evidence exists to support the claim that caloric for caloric one hypocaloric diet will lead to a greater weight loss than another. The relationship between the patient and the therapist, plus patient education and encouragement, are more important to success than are the specific dietary constituents. The major virtue of "fad" diets

is that patients are usually motivated to try them, at least initially, and patient cooperation is often better. Provided a particular diet is not harmful, probably the best course for the therapist is to maintain flexibility in the treatment program. Nevertheless, diets markedly deficient in any major class of foodstuff are to be avoided. For example, whole-food diets that are exceedingly low in carbohydrate are by nature high in fat and, depending on the type and quantity of fat ingested, may lead to hypercholesterolemia. The major virtue of a low-carbohydrate diet is the attendant ketosis (ketone bodies have a central anorexiant effect). This provided part of the rationale for the widely touted liquid or powdered protein diets that were previously popular. These diets have been dubbed "protein-sparing modified fasts," and claims were made that they allowed drastic long-term caloric restriction without inducing negative nitrogen balance. These claims have not been substantiated, nor has it been shown that the diets lead to a greater degree of fat tissue weight loss than mixed diets of equal caloric value. Basically a calorie is a calorie whether it comes from protein, carbohydrate, or fat. Furthermore, deaths have been reported in otherwise healthy individuals participating in such long-term dietary programs, even under medical supervision. This has been attributed to the fact that some of these diets contain mostly collagen-derived protein of low biologic value. Other very low caloric diets involve formula preparations containing 500 to 800 kcal/d, with 50 to 80 g of high-quality protein. The remaining calories consist of carbohydrate and fat. Vitamin and micronutrient supplements are incorporated in the formula or provided as an added supplement. Such high-quality low-calorie diet formulas lead to relatively rapid weight loss but should not be taken continuously as the sole caloric source for more than 6 weeks. In the absence of coexisting diseases such as gout, renal insufficiency, cardiac arrhythmias, etc., such diets are safe when taken under medical supervision. Such very low caloric diets are contraindicated in pregnant women and growing children.

Prior to therapy it is wise to warn patients that when caloric restriction is started, there is usually a marked initial weight loss, in large part due to fluid loss, but such rapid rates of loss will not persist. Likewise, positive shifts in fluid balance can sometimes mask loss of adipose mass, a fact that can sometimes be demonstrated to the patient's satisfaction by recording skin-fold thickness at periodic intervals.

Total-starvation diets have been advocated for the treatment of obesity; provided gout, renal insufficiency, and ketosis-prone diabetes are not present, short-term (2- to 3-day) fasts are usually well tolerated. Ketonemia and hyperuricemia regularly develop during starvation but rarely lead to acidosis or gout. Because of these potential complications, total fasting should be carried out only under medical supervision. Probably the major usefulness of total fasting is as a motivational aid at the beginning of a dietary program or when weight loss has stopped. Even though much of the weight loss during short-term fasting represents fluid, this weight loss can be encouraging to frustrated patients and motivate them to improve compliance with the long-term weight reduction program.

The major problem in the treatment of obesity is not weight reduction but maintenance of the reduced weight. Provided the therapist works hard and long enough, most motivated patients can eventually lose weight. Unfortunately, only the rare patient maintains the weight loss permanently. Obesity is an eating disorder, and the underlying mechanisms are not reversed by limiting food intake.

Behavior modification In recognition of the problems involved, the techniques of behavior modification have been devised to treat abnormal patterns of eating behavior. Many studies demonstrate that obese individuals respond less well than normal individuals to internal cues that regulate eating behavior such as gastric contractions, fear, and previous food ingestion. Conversely, obese subjects overrespond to external cues such as taste, smell, food attractiveness, food abundance, and the ease of obtaining food. Given the fact that the obese individual is unusually susceptible to external stimuli, food intake may be altered by changing the pattern and nature of these

external cues, and this is the major premise underlying the behavior modification approach to weight reduction.

Behavior modification begins with a detailed individual history of the patient's eating patterns with respect to time of day, length of eating period, place of ingestion (restaurant, dining table, standing in front of open refrigerator), simultaneous activities (watching television, reading, idleness), emotional state, companions (relatives, friends, or alone), and finally the kinds and quantities of foods ingested. Once this detailed record is obtained, the therapist and patient can design specific behavioral changes aimed at disrupting or aborting recurring behavior patterns which initiate or prolong abnormal eating activity. As examples: if a patient eats in response to certain emotional states, then other activities can be substituted when the patient perceives such a state; if the patient snacks frequently from readily available food storage areas (refrigerators, cookie jars, etc.), then he or she is encouraged to eat only while sitting down at a table with a fixed place setting; if eating frequently occurs while watching television alone, then efforts to avoid this activity can be initiated. Many other examples of specific and general interventions could be given. Results with behavior modification techniques indicate that many patients can maintain long-term weight reduction providing the new behavior patterns are truly "learned."

Exercise Exercise has a place in any weight reduction program. However, the importance of exercise in terms of caloric balance must be clearly understood. Even moderate daily exercise would not lead to a large enough increase in energy expenditure to alter significantly the initial rate of weight reduction (Table 72-1). This does not mean exercise is unimportant in weight reduction, since even modest increases in caloric expenditure can lead to large long-term differences in caloric balance, provided exercise is performed on a regular basis. For example, a daily increase in caloric expenditure of 1250 kJ (300 kcal) over a period of 4 months could lead to a 4.5-kg weight loss. More importantly, incorporation of regular exercise into the overall weight reduction program improves the chances that the patient will maintain the weight loss.

Drugs Two classes of drugs are frequently used in the treatment of obesity: anorexiant and thyroid hormone supplements. The addition of levothyroxine or triiodothyronine to a weight reduction program is ineffective in promoting adipose tissue loss and, if anything, accentuates lean tissue loss and causes negative nitrogen balance. In susceptible individuals, cardiotoxicity may occur. Thus, unless clear-cut hypothyroidism is present, thyroid supplementation has no role in the treatment of obesity.

The major anorexiant is amphetamine-like agents that presumably exert their effect at the level of the hypothalamus. They probably have a modest effect in promoting short-term weight loss in some individuals. However, they are effective only for short periods, and problems of habituation, addiction, and drug abuse limit their usefulness. Two anorexiant, diethylpropion and fenfluramine, may be less addictive and, therefore, somewhat more useful. However, none of these agents treats the underlying eating disorder, and they are of little use in maintenance of weight reduction.

Injections of human chorionic gonadotropin (hCG) have been tried as an adjunct to weight reduction, but no evidence exists to indicate a beneficial effect. The primary effectiveness of the hCG-diet program is due to the calorically restricted diet, frequent physician contact, and placebo effects. Comparable weight loss is achieved if saline injections are substituted for hCG, suggesting a placebo or physiologic effect of the act of parenteral injection.

Jejunioileal shunt Small-bowel bypass is an effective means of achieving weight reduction in morbidly obese patients. However, it is an experimental procedure and should be attempted only in institutions where a trained team is committed to regular, systematic, and long-term follow-up. Because of accompanying morbidity and mortality most such institutions have abandoned this form of surgery in favor of the more benign and effective gastric plication or bypass approach described below.

The most common operative procedures for the jejunioileal shunt

TABLE 72-1 Energy equivalents of food calories expressed in minutes of activity

Food	Energy value, kJ (kcal)	Activity				
		Walking*	Riding bicycle†	Swimming‡	Running§	Reclining¶
Apple, large	422 (101)	19	12	9	5	78
Bacon, 2 strips	401 (96)	18	12	9	5	74
Beer, 1 glass	477 (114)	22	14	10	6	88
Bread and butter	326 (78)	15	10	7	4	60
Carbonated beverage, 1 glass	444 (106)	20	13	9	5	82
Carrot, raw	176 (42)	8	5	4	2	32
Cheese, cottage, 1 tbsp	113 (27)	5	3	2	1	21
Chicken, fried, 1/2 breast	971 (232)	45	28	21	12	178
Cookie, chocolate chip	213 (51)	10	6	5	3	39
Egg, fried	460 (110)	21	13	10	6	85
Ham, 2 slices	699 (167)	32	20	15	9	128
Ice cream, 1/2 qt	808 (193)	37	24	17	10	148
Mayonnaise, 1 tbsp	185 (44)	18	11	8	5	71
Milk, skim, 1 glass	339 (81)	16	10	7	4	62
Milk shake	1762 (421)	81	51	38	22	324
Orange, medium	285 (68)	13	8	6	4	52
Pancake with syrup	519 (124)	24	15	11	6	95
Peas, green, 1 cup	234 (56)	11	7	5	3	43
Pizza, cheese, 1/2	753 (180)	35	22	16	9	138
Potato chips, 1 serving	462 (108)	21	13	10	6	83
Sandwiches:						
Hamburger	1456 (350)	67	43	31	18	269
Tuna fish salad	1163 (278)	53	34	25	14	214
Sherbet, 1 qt	741 (177)	34	22	16	9	136

* Energy cost of walking for 70-kg individual = 22 kJ (5.2 kcal)/min.

† Energy cost of riding bicycle = 34 kJ (8.2 kcal)/min.

‡ Energy cost of swimming = 47 kJ (11.2 kcal)/min.

§ Energy cost of running = 81 kJ (19.4 kcal)/min.

¶ Energy cost of reclining = 5 kJ (1.3 kcal)/min.

involve end-to-end or end-to-side anastomosis of about 38 cm of proximal jejunum to 10 cm of terminal ileum. Weight loss is initially rapid, reaching a plateau at 18 to 24 months. While all patients lose weight, few return to ideal weight. The mean weight loss is about 30 to 50 percent of initial excess weight, leaving patients still about 50 percent overweight once a steady state is reached. Although some degree of malabsorption occurs, the major portion of the weight loss is due to decreased food intake.

Teams still performing this surgery select patients who are at least 50 kg overweight and in whom adequate attempts at medical management have failed repeatedly. Because of postoperative morbidity, older patients (>50 years) and psychologically unstable individuals are usually excluded.

The overall surgical mortality ranges from 0.5 to 7.8 percent with an average of around 4 percent. Mortality is inversely related to the experience of the surgical team. The major postoperative morbidity is related to wound infection and thromboembolism. The common serious medical complications are cirrhosis and hepatic failure, nephrolithiasis, electrolyte imbalances, cholelithiasis, and arthritis (Table 72-2). Severe liver disease probably occurs in 5 percent of patients, and milder degrees of hepatic dysfunction are more common. The long-range implications of mild hepatic abnormalities are unknown. Possible causes of liver damage following small-bowel bypass include (1) protein and particularly essential amino acid deficiency, (2) accumulation of hepatotoxic, secondary bile salts, and (3) release of unknown toxic substances from the excluded bowel. Hypokalemia is most likely secondary to diarrhea. Persistent deficiency of calcium and magnesium can result from malabsorption and must be treated with appropriate replacement. Transient depression of plasma 25-hydroxyvitamin D levels may also contribute to abnormal mineral metabolism. Nephrolithiasis occurs in up to 30 percent of patients and is due to hyperoxaluria secondary to calcium malabsorption. It can be treated by calcium supplements and a low oxalate intake. Migratory polyarthritis occurs in up to 6 percent of patients and may be due to circulating immune complexes. This operation is now rarely performed, in part due to the decision of many insurance companies not to render compensation for this procedure.

Gastric surgery Gastroplasty establishes a small upper gastric remnant connected to a larger lower gastric pouch by a narrow 1- to 1.5-cm channel. Gastric bypass excludes the lower 90 percent of the stomach pouch and maintains intestinal continuity of the upper 10 percent via a retrocolic gastrojejunostomy. Both of these procedures

TABLE 72-2 Complications of bypass surgery

Complication	Percentage
Early	
Perioperative mortality	2-6
Thromboembolic disease	1-5
Wound infection	2-5
Renal failure	3
Severe nausea, vomiting	3
Wound dehiscence	1-3
Long-term	
Urinary calculi	3-10
Severe electrolyte imbalance	5-8
Acute cholecystitis	0-5
Progressive liver disease	2-4
Intestinal obstruction	?
Peptic ulcer	1-2
Osteoporosis	?
Tuberculosis	1
Other	
Diarrhea	100
Weakness	80
Hypokalemia	80
Hypoproteinemia	50
Vomiting	50
Thirst	50
Hypocalcemia	30
Anthrax	15
Incisional hernias	3
Hyperuricemia	<10
Anemia	<10

cause patients to limit food intake by delaying gastric emptying and providing a small gastric reservoir so that fullness is experienced after a small meal. Weight loss with these procedures is comparable with that achieved with small-bowel bypass operations but without the complications related to malabsorption, diarrhea, and hepatic dysfunction. The procedure can be reversed if a decision to restore normal anatomy is made at a later time. For these reasons, gastropasty is frequently performed for the surgical treatment of morbid obesity in patients who have failed standard weight loss regimens.

SUMMARY For most patients obesity is an eating disorder, and a major hope for effective long-term treatment of this disease lies in understanding the causes of overeating. No single etiology explains all cases, and different causes exist for different individuals. At present a variety of techniques are available to effect initial weight loss. Unfortunately, initial weight loss is not the real therapeutic goal. Rather, the problem is that most obese patients eventually regain their weight. An effective means to sustain weight loss is the major challenge in the treatment of obesity today. The technique of behavioral modification, when professionally and rigorously applied, is the best tool for this task. As information develops concerning the hypothalamic "set point," or *adipostat*, and the factors that regulate it, other therapies may emerge that will effect long-term correction of abnormal eating patterns.

REFERENCES

- BRAJ GA: Current status of intestinal bypass surgery in the treatment of obesity. *Diabetes* 26:1072, 1977
- GRAY IS: Treatment of obesity: Overview. *Diabetes/Metabolism Rev* 4:653, 1988
- FOSTER DW: Eating disorders: Obesity and anorexia nervosa, in *Williams Textbook of Endocrinology*, 7th ed, ID Wilson, DW Foster (eds). Philadelphia, Saunders, 1985, p 1081
- HASHIM SA, PERIKOS K: Food intake behavior in man: Implications for treatment of obesity. *Clin Endocrinol Metab* 5:503, 1976
- HENRY RR et al: Metabolic consequences of very low calorie diet therapy in obese non-insulin dependent diabetic and non-diabetic subjects. *Diabetes* 35:155, 1986
- HORTON ES, DANFORTH E Jr: Energy metabolism and obesity, in *Diabetes Mellitus and Obesity*, SJ Bleicher, BN Brodoff (eds). Baltimore, Williams & Wilkins, 1981, p 261
- KOLTERMAN OG et al: Mechanisms of insulin resistance in human obesity. Evidence for receptor and postreceptor defects. *J Clin Invest* 65:1272, 1980
- MAHON GV: The influence of obesity on health. *N Engl J Med* 291:226, 1974
- NATIONAL INSTITUTES OF HEALTH CONSENSUS DEVELOPMENT PANEL ON THE HEALTH IMPLICATIONS OF OBESITY: Health implications of obesity. *Ann Intern Med* 103:147, 1985
- OLEFSKY JM et al: Insulin action and insulin resistance in obesity and non-insulin dependent, type II diabetes mellitus. *Am J Physiol* 243:E15, 1982
- SALANS L: The obesities, in *Endocrinology and Metabolism*, 2d ed, P Felig et al (eds). New York, McGraw-Hill, 1987, chap 21, p 1203
- STUNKARD AJ et al: An adoption study of human obesity. *N Engl J Med* 314:193, 1984
- The Surgeon General's Report on Nutrition and Health. US Department of Health and Human Services Public Health Service (DHRHS PHS) Publication 88-50210, 1988
- WOO R et al: Regulation of energy balance, in *Annual Review of Nutrition*, vol 5. Palo Alto, Annual Reviews Inc, 1985, pp 411-433

73 ANOREXIA NERVOSA AND BULIMIA

DANIEL W. FOSTER

Anorexia nervosa and bulimia are eating disorders in young, previously healthy women who develop a paralyzing fear of becoming fat. The population at risk consists largely of white women from middle- and upper-class backgrounds. The disorders rarely occur in black or oriental women, are unusual in the poor, and are almost never seen in men. The driving force is the pursuit of thinness, all other aspects of life being secondary. In the anorexia nervosa syndrome this aim is achieved primarily by radical restriction of caloric intake, the end result being emaciation. In bulimia massive binge eating is followed by vomiting and excessive use of laxatives. Weight loss in bulimic

subjects is not great despite the obsession with food. Some authors consider anorexia nervosa and bulimia to be distinct illnesses, while others classify bulimia as a variant of anorexia nervosa. Overlap syndromes exist since emaciated patients fulfilling the criteria of true anorexia nervosa may exhibit bulimic behavior, while subjects with bulimia often pass through a phase of anorexia. In this chapter it is assumed that the two disorders are different clinical expressions of a primary psychologic obsession with body weight.

PREVALENCE Estimates of prevalence for anorexia nervosa range from 0.4 to 1.5 per 100,000 population. In adolescent white girls from middle- or upper-class families rates as high as 1 per 100 have been reported. Prevalence is believed to be increasing. Subclinical variants may occur in up to 5 percent of the socioeconomic group at highest risk. The incidence of bulimia is less certain. Vomiting after eating may occur in as many as 18 percent of women college students. The frequency of self-induced vomiting is probably 1 to 2 percent, but the full-blown bulimic syndrome is less frequent.

DIAGNOSIS The diagnosis of both anorexia nervosa and bulimia is made on clinical grounds. No specific diagnostic tests exist. For many years the criteria of Feighner et al (Table 73-1) were the basis for diagnosis in research studies. Less strict requirements were formulated for the American Psychiatric Association's *Diagnostic and Statistical Manual of Mental Disorders* (revised, third edition; DSM-III-R.)

In the revised criteria the weight loss required for diagnosis was decreased from 25 to 15 percent of expected or ideal weight. Three other requirements were listed: intense fear of gaining weight or becoming fat even when underweight; disturbance in the way body weight, size, or shape is experienced such that the individual "feels fat"; and, in women, either primary amenorrhea or secondary amenorrhea for at least three consecutive periods. The Feighner criteria remain useful, although it seems reasonable to substitute the 15 percent figure for weight loss. In actuality the spectrum of restricted eating ranges from a mild disorder of little consequence to life-threatening starvation. For this reason neither set of criteria is definitive.

The uniqueness of the disturbance in body image in patients with eating disorders has been questioned, and some authorities have recommended its omission on the grounds that many normal young women demonstrate the same perceptual distortion. In practice a presumptive diagnosis of anorexia nervosa is justified if the following elements are elicited: (1) a history of major weight loss; (2) absence of organic disease sufficient to account for weight loss; (3) absence of severe primary psychiatric illness that might account for failure to eat; (4) extreme restriction of food intake with or without intermittent induction of vomiting; (4) ritualized exercise; and (5) denial of hunger, fatigue, or emaciation.

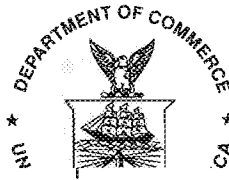
The criteria for the diagnosis of bulimia in DSM-III-R appear to be less useful. The picture is that of a normal- or near-normal-weight subject whose life is dominated by gorging and regurgitation in the absence of profound weight loss.

ETIOLOGY The cause of anorexia nervosa and bulimia is unknown. Although primary dysfunction of the hypothalamus has been

TABLE 73-1 Criteria for the diagnosis of anorexia nervosa

- 1 Onset prior to age 25
- 2 Anorexia with weight loss of at least 25 percent of original body weight
- 3 Distorted attitude toward eating, food, or weight that overrides hunger, admonitions, reassurances, and threats
- 4 No known medical illness that could account for the weight loss
- 5 No other known psychiatric disorder
- 6 At least two of the following manifestations:
 - a Amenorrhea
 - b Lanugo hair
 - c Bradycardia (persistent resting pulse of 60 beats per minute or less)
 - d Periods of overactivity
 - e Episodes of bulimia
 - f Vomiting (may be self-induced)

SOURCE: After Feighner et al.



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**BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES**

Paper No. 101009

Application Number: 08/870,762
Filing Date: 06/06/1997
Appellant: Duft *et al.*

For Appellant
Steven C. Koerber

EXAMINER'S ANSWER

This is in response to Appellant's brief on appeal filed 08/07/2008.

(1) Real Party in Interest

A statement identifying the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

The Examiner is aware of a related pending appeal in application 09/445,517, which is a continuation-in-part of the instant application, which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

(3) Status of Claims

The statement on the status of the claims contained in the brief is correct.

This appeal involves claims 1-7 and 9-17.

Claim 8 was previously canceled.

(4) Status of Amendment After-Final

The Appellant's statement of the status of after-final amendment contained in the brief is correct.

(5) Summary of Claimed Subject Matter

The summary of the claimed subject matter contained in the appeal brief is correct.

(6) Grounds of Rejection to be Reviewed on Appeal

The Appellants' statement of the grounds of rejection to be reviewed on appeal is correct.

Withdrawn Rejection(s)

(i) The following ground of rejection is not presented for review on appeal because the rejection has been withdrawn upon further consideration and/or based on Appellants' arguments presented in the appeal brief.

The rejection of claims 3 and 17 made in paragraph 29 of the Office Action mailed 02/11/08 and maintained in paragraph 14 of the Office Action mailed 04/30/08 under 35 U.S.C § 112, first paragraph, as being non-enabled with regard to the full scope, is withdrawn.

(ii) The as-evidenced-by reference of Rink *et al.* (US 5,739,106) ('106) cited in the rejection of claims 7, 14 and 16 made under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 11 and 13 of US patent 5,321,008 issued to Beumont *et al.* ('008) as evidenced by Tsanev (*Vutr. Boles* 23: 12-17, 1984, abstract) has been withdrawn. The rejection however is maintained.

(7) Claims Appendix

The copy of the appealed claims contained in the Appendix to the brief is correct.

(8) Evidence Relied Upon

The following evidence is relied upon by the Office in the rejection of the claims under appeal.

- 1) US patent 5,686,411 ('411) issued to Gaeta *et al.* and published 11/11/1997
- 2) Tsanev A. *Vutr. Boles*. 23: 12-17, 1994, abstract cited on PTO-892 mailed 06/01/06
- 3) US patent 5,321,008 ('008) issued to Beumont *et al.* and published 06/14/1994
- 4) US patent 5,739,106 ('106) issued to Rink *et al.* and published 04/14/1998
- 5) WO 92/20367 of Rink *et al.*, published 11/26/1992
- 6) US patent 5,364,841 ('841) issued to Cooper *et al.*, published 11/15/1994
- 7) US patent 5,280,014 ('014) issued to Cooper *et al.*, published 01/18/1994
- 8) Rattner *et al. Exp. Clin. Endocrinol. Diabetes* 113: 199-204, 2005 (Rattner, 2005)

- 9) Baron *et al.* *Current Drug Targets – Immune, Endocrine & Metabolic Disorders* 2: 63-82, 2002
- 10) US patent 5,175,145 ('145) issued to Cooper *et al.*, published 12/29/1992
- 11) WO 96/40220 ('220) of Kolterman *et al.*, published 12/19/1996
- 12) Kolterman *et al.* *Diabetologia* 39: 492-499, 1996 (Kolterman *et al.*, 1996)
- 13) Itasaka *et al.* *Psychiatr. Clin. Neurosci.* 54 : 340-341, 2000
- 14) Thompson *et al.* *Diabetes* 46: Suppl. 1, page 30A, 0116, May 02, 1997
- 15) Ratner *et al.* *Diabetes Technol. Ther.* 4 : 51-61, 2002
- 16) Olefsky JM. In: *Harrison's Principles of Internal Medicine*, (Ed) Wilson *et al.*, 12th Edition, McGraw-Hill Book Company, pages 411-416, 1961

(9) Grounds of Rejections

The following grounds of rejections are applicable to the appealed claims.

Rejection(s) under 35 U.S.C § 112, First Paragraph (Scope of Enablement)

(A) Claims 1, 2, 4-7 and 9-16 are rejected under 35 U.S.C § 112, first paragraph, because the specification, while being enabling for a method of reducing the body weight of an insulin-taking type 2 diabetic human subject having a body weight not varying more than 45% from the desirable weight, by subcutaneous administration to said subject, an amount of the amylin agonist analogue species, ^{25,28,29}Pro-h-amylin (SEQ ID NO: 1), i.e., pramlintide, wherein said pramlintide is not in conjunction with another obesity relief agent, and wherein said amount of the pramlintide significantly reduces the mean body weight of said human subjects after four weeks of said treatment compared to the mean body weight of said subject prior to said treatment, does not reasonably provide enablement for a method of treating obesity in any human subject including a non-diabetic human subject in need of treatment for obesity, or a diabetic human subject in need of treatment for obesity who is not on insulin therapy, comprising or consisting of administering a generic amylin, a generic amylin agonist other than calcitonin or CGRP, or any amylin agonist analogue other than pramlintide (SEQ ID NO: 1), as claimed in a broad sense. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with the claims.

Instant claims are evaluated based on *Wands* factors. Many of the factors regarding undue experimentation have been summarized in *In re Wands*, 858 F.2d 731, 8 USPQ2d 1400 (Fed. Circ. 1988) as follows:

- The quantity of experimentation necessary (time and expense);
- The amount of direction or guidance presented;
- The presence or absence of working examples of the invention;
- The nature of the invention;
- The state of the art;
- The relative skill of those in the art;
- The predictability or unpredictability in the art; and
- The breadth of the claims.

In the instant application, the nature of the invention is pertinent to the treatment of obesity in a human subject in need of such treatment comprising or consisting of administering an amylin, an amylin agonist, or an amylin agonist analogue composition or compound in an amount effective to inhibit weight gain or induce weight loss in said subject. As described in the instant specification, the state of the art recognizes obesity or adiposity to be a 'chronic disease' that is highly prevalent in modern society which is strongly associated with multiple conditions including diabetes mellitus, insulin resistance, hypertension etc. The limitation 'obesity' encompasses diabetes-associated obesity, non-diabetes-associated obesity, morbid obesity, aging-associated obesity, insulin requiring obesity, obesity associated with family genetics, obesity due to hypernutrition etc. With regard to the breadth, the method claimed in claims 1, 2, 4, 5, 7 and 14-16 does not require that a specific amount of the recited amylin or amylin agonist be administered, whereas the method of claims 6 and 9-13 recite specific amounts of amylin or amylin agonist be administered. The method of claims 1, 2, 5, 7 and 13-16 does not require that the recited amylin or amylin agonist be administered via a specific route, whereas claim 4 recites that the administration is by subcutaneous route. Claims 1, 2, 14 and 16 encompass administration of any amylin or amylin agonist by any route, in any quantity, and any number of times per day, to any human subject in need of treatment for obesity for any length of time.

The step recited in claim 1 'consists of administering' to said human subject, an amount effective to inhibit weight gain (i.e., maintain the existing weight) or an amount effective to induce weight loss in said human subject, of a composition 'comprising' a pharmaceutically acceptable carrier and an amylin or an amylin agonist. Such an administration step *excludes* administration of

any other substance, simultaneous insulin administration, or insulin administration before or after the administration of an amylin, amylin agonist, or an amylin agonist analogue. Furthermore, because of the open claim language 'comprising', the composition recited in claims 1 and 2 is allowed to comprise one or more obesity relief agents, or any other compounds in addition to amylin or an amylin agonist. As claimed currently, 'an amount effective to inhibit weight gain or induce weight loss in said human subject' is not the amount of the recited amylin or the amylin agonist, but of the composition that 'comprises' an amylin, amylin agonist, or an amylin agonist analogue plus a pharmaceutically acceptable carrier plus any other element that is 'comprised' within the composition, including another anti-obesity agent. 'Therapeutically effective amounts' of an amylin, an amylin agonist, or an amylin agonist analogue, for use in the control of obesity are described in the specification as 'those that decrease body weight', but are not described as amounts that inhibit weight gain, i.e., an amount that maintains the weight as existed prior to the treatment. See last full sentence on page 22 of the instant specification. The method of treating obesity in a human subject in need of treatment for obesity as claimed in the independent claim 7 'comprises' administering to said subject an amount of a composition comprising a pharmaceutically acceptable carrier and an obesity relief agent 'consisting' of an amylin or an amylin agonist in an amount effective to inhibit weight gain or induce weight loss in said human subject and is effective to treat obesity. The method of treating obesity in a human subject in need of treatment for obesity as claimed in the independent claim 14 'comprises' administering to said subject a compound selected from the group consisting of an amylin, an amylin agonist, and salts thereof, wherein the compound, including the salt compound, is administered in an amount effective to treat obesity by inhibiting weight gain or inducing weight loss, and wherein said compound is not administered in conjunction with another obesity relief agent. The method of treating obesity in a human subject in need thereof as claimed in the independent claim 16 'comprises' administering to said subject an effective amount of a 'composition consisting essentially of an amylin or an amylin agonist, wherein said amount' of the composition is effective to treat obesity by inhibiting weight gain or inducing weight loss in said subject. The instant disclosure lacks a specific definition for the limitation 'a composition consisting essentially of an amylin or an amylin agonist' as to what it excludes or includes, and therefore one cannot envisage whether or not the composition includes or excludes an element such as insulin, glucagon, an anti-

diabetic agent, or a gastric emptying agent etc. The limitation 'a human subject ... in need of treatment for obesity' encompasses an overweight, moderately obese, morbidly obese, diabetic and non-diabetic obese, insulin-requiring and insulin non-requiring obese human subject as well as a human subject with natural aging-associated obesity. The limitations 'amylin agonist' and 'amylin agonist analogue' broadly encompass a myriad of compounds, including a peptide and a nonpeptide compound (see paragraph bridging pages 13 and 14 of the original specification), non-human amylin, amylin having amino acid modifications or substitutions, variants of amylin, and the art-accepted amylin agonists such as calcitonin and CGRP (see lines 45-47 in column 7 of US patent 5,739,106 and claims 3 and 10 of US 5,175,145) etc.

With regard to scope of enablement, a review of the instant specification indicates that Examples 2-4 and 9-20 are not enabling of the claimed method of treatment. Instead, these Examples describe how to prepare selective amylin agonist analogues. Example 5 pertains to the evaluation of *in vitro* binding of compounds to amylin receptors whereas Example 6 pertains to the determination of amylin agonist activity of the compounds as measured by soleus muscle assay. Examples 7 and 8 describe methods of measuring gastric emptying using phenol red and tritiated glucose gastric emptying assays. What are claimed however are not amylin agonist analogues, or a method of making them, or using them in *in vitro* assays as described in Examples 2-4 and 9-20 of the instant specification, but a method of treating obesity in a mammal in need of treatment for obesity by administering *in vivo* a weight gain-inhibiting effective amount or a weight loss-inducing effective amount of an amylin, amylin agonist, or amylin agonist analogue. Example 1 of the instant specification indicates that the human subjects used in the instant invention are those with a history of type 2 diabetes mellitus, who *required* insulin treatment for at least 6 months prior to the pre-screening visit. Body weight-wise, i.e., obesity-wise, these patients are described as having a body weight not varying more than 45% from the 'desirable weight' before admission into the study based upon Metropolitan Life Tables. The only amylin agonist species or amylin agonist analogue species that was administered to these type 2 diabetic patients was ^{25,28,29}Pro-h-amylin (SEQ ID NO: 1), also known as pramlintide. Groups of patients were given separate mealtime pramlintide, 30 micrograms QID; 60 micrograms QID, or 60 micrograms TID subcutaneously before 15 minutes of each meal three to four times a day. Patients *remained on their insulin, usual diet, and exercise regimens* and

therefore the method 'comprised' administration of pramlintide as explained above, along with the administration of insulin. The study period was limited to four weeks, i.e., 28 days, and the outcome was determined by comparing, at the end of four weeks, the mean body weight of the treated diabetic subjects with the mean body weight of the subject prior to the treatment. Thus, the originally filed specification at pages 30-31 and Table I describes a *statistically significant reduction* in the mean baseline weight seen after the subcutaneous administration of 60 micrograms TID or 60 micrograms QID of one specific amylin agonist species or amylin agonist analogue species, pramlintide (SEQ ID NO: 1), to type 2 diabetic subjects for four weeks, wherein said pramlintide administration was *accompanied* with the continued use of insulin. The method as described in the originally filed specification thus comprised insulin treatment *and* the administration of a specific dose of pramlintide in type 2 diabetic patients via a specific route. The decrease in body weight observed was statistically significant compared to the body weight of those type 2 diabetes patients who were treated with insulin alone. However, this single enabled embodiment is not representative of the full scope of the claims which broadly encompasses the administration of any amylin, any amylin agonist, or any of a plethora of non-pramlintide amylin agonist analogues in the treatment of obesity in diabetic and non-diabetic patients *not* on insulin treatment. While there is no requirement for Applicants to enable all of the amylin species, amylin agonist species, or amylin agonist analogue species encompassed within the claimed invention, enablement of a reasonable or representative number such species in the claimed method is required. This is critically important because at the time of the invention, there was no predictability that if one used an amylin, amylin agonist, or a non-pramlintide amylin agonist analogue in place of Applicants' pramlintide (SEQ ID NO: 1) in type 2 diabetic or non-diabetic overweight or obese subjects who are on or not on insulin treatment, or in morbidly obese human subjects who are on or not on insulin therapy, the administered amylin, amylin agonist, or non-pramlintide amylin agonist analogue would bring about significant or clinically meaningful weight loss-inducing, weight gain-inhibiting, or obesity-relieving effect. Neither the state of the art *at the time of the invention*, nor the instant specification as originally filed, provides specific guidance and direction with regard to the use of a generic amylin, or a non-pramlintide or non-calcitonin amylin agonist, or a non-pramlintide amylin agonist analogue to treat obesity in a generic human subject in need of treatment for obesity.

Upon consideration of the evidence as a whole and analysis of all of the *Wands* factors, the instantly claimed methods are viewed as being non-enabled with regard to the full scope. It should be noted that the scope of the required enablement varies inversely with the degree of predictability involved. A single embodiment may provide broad enablement in cases involving predictable factors. However, in applications directed to inventions in arts where results are unpredictable, the disclosure of a single species does not provide an adequate basis to enable generic claims. MPEP § 2164.03. In cases involving unpredictable factors, such as most chemical reactions and physiological activity, more may be required. *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970) (contrasting mechanical and electrical elements with chemical reactions and physiological activity). See also *In re Wright*, 999 F.2d 1557, 1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993); *In re Vaeck*, 947 F.2d 488, 496, 20 USPQ2d 1438, 1445 (Fed. Cir. 1991). This is because it is not obvious from the disclosure of one species, what other species will work. In the instant case, it is not obvious from the disclosure of the administration of pramlintide species in the treatment of obesity in type 2 diabetic humans, what other amylin species, non-pramlintide species, or salts thereof would work in treating obesity in diabetic or non-diabetic humans in need of treatment of obesity, with or without co-administration of insulin. It should be noted that predictability or unpredictability is one of the *Wands* factors to be considered for enablement or lack thereof under 35 U.S.C § 112, first paragraph. The instantly claimed invention is in an area of art that is unpredictable. Amylin, a sufficient number of non-pramlintide amylin agonist analogues, and salts thereof, are not enabled as obesity relief agents in the instantly claimed method. Mere recitation of representative examples of amylin, amylin agonists, or amylin agonist analogues of the claimed genus together with a statement applicable to the genus as a whole is not sufficient to enable the full scope of the claimed methods, because one skilled in the art would not expect that the claimed genus could be used in that manner without undue experimentation. A specification disclosure which contains a teaching of the manner and process of making and using an invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented must be taken as being in compliance with the enablement requirement of 35 U.S.C. 112, first paragraph, *unless* there is a reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support. Assuming that sufficient reason for such doubt exists, a rejection for failure to

teach how to make and/or use will be proper on that basis. *In re Marzocchi*, 439 F.2d 220, 224, 169 USPQ 367, 370 (CCPA 1971).

In the instant case, one of the reasons for doubting the objective truth of the statements comes from Appellants' own statement. For example, Appellants have readily acknowledged previously that administration of amylin would have lead to *weight gain* rather than *weight decrease* as was known at the time of the invention via the disclosure of US patents 5,364,841 and 5,280,014. Applicants have expressly stated previously that at the time of the invention, amylin was administered to patients suffering from *anorexia* or *a similar condition* 'in order to increase weight'. See pages 7 and 8 of Appellants' amendment filed 03/22/99. Thus, at the time of the invention, amylin at a dose varying from about 0.1 to 10 mg (which dose encompasses the doses recited in the instant claims, including claims 6 and 9-13) was administered to treat patients suffering from *anorexia* or *patients deficient in adipose tissue*. See also claims and page 13 of Rink *et al.* (WO 9220367). This alone is *prima facie* evidence for the lack of scope of enablement of the instantly claimed method of treating obesity as claimed comprising administration of amylin as claimed. Therefore, despite the level of skill in the art and despite the structural relatedness to pramlintide, there is no predictability that administration of a dose of amylin varying from about 0.1 to 10 mg to a human patient in need of treatment for obesity would have resulted in inhibition of weight gain or induction of weight loss. Instead, one of skill in the art would have expected induction of weight gain upon administration of amylin as acknowledged by Appellants. With the weight gain-increasing effect of amylin known at the time of the invention, one of skill in the art would have reasonably expected amylin and the innumerable number of non-pramlintide amylin agonists or amylin agonist analogues encompassed within the scope of the instant claims, to be therapeutic for anorexia. The administration of amylin or a non-pramlintide amylin agonist analogue would *not* have predictably brought about weight gain-inhibiting or weight loss-inducing effect. Thus, in view of level of skill, the state of the art at the time of the invention, and the information in the specification, one of skill would *not* expect that the recited genus could be used in that manner without undue experimentation. Therefore, the considerable amount of experimentation needed in the instant case is not merely routine, but undue in view of the unpredictability and the lack of evidence enabling the full scope of the invention.

Furthermore, with regard to the state of the art at the time of the invention, Appellants have previously gone on the record with the following (see pages 9, 13 and 14 of Appellants' Appeal Brief filed July 2000) [Emphasis in original]:

.... THE RINK PATENT PROVIDES THAT AMYLIN AND AMYLIN AGONISTS ADMINISTERED AS DESCRIBED AND CLAIMED IN THE PRESENT APPLICATION HAVE "NO MEASURABLE EFFECT" ON FOOD INTAKE.

.... the Rink patent reports that a 1.0 µg/kg dose (**equivalent to about 70µg/dose in an adult human**) had no effect on food intake. [Emphasis in bold added]

The Rink patent that is being referred to *supra* by Appellants is US 5,739,106. Note that the above-mentioned about 70 µg/dose in an adult human is encompassed within the therapeutic amount range of about 0.01 to about 5 mg, or about 0.05 to about 2 mg of amylin, as recited in instant claims 12-14. Thus, in view of the above-cited acknowledgment of the failure of amylin to have any effect on food intake, one of skill in the art would look into Appellants' specification for specific guidance and direction for the use of amylin in treatment of obesity. However, the instant specification fails to show that human or non-human amylin or a salt thereof, or a composition comprising, consisting of, or consisting essentially of the same, was in fact stable, soluble and/or non-aggregating enough to be 'therapeutic' in a method of treating obesity upon administration in any amount and by any route, with or without concurrent insulin therapy, to a diabetic or non-diabetic human subject in need of treatment for obesity. This is important because with regard to the therapeutic use of amylin, the state of the art indicates difficulty, undesirable pharmacological properties, and impracticability of using amylin, including human amylin, clinically as 'a therapeutic agent'. For instance, Baron *et al.* (*Current Drug Targets – Immune, Endocrine & Metabolic Disorders* 2: 63-82, 2002) taught the following with regard to the clinical use of amylin as a therapeutic agent:

Clinical use of amylin as a therapeutic agent is considered impractical because of its instability in solution and its propensity to aggregate and adhere to surfaces, properties that hamper the manufacturing, formulation, and storage of this peptide as a drug. Pramlintide is a synthetic, equipotent analogue of human amylin in which the undesirable pharmacological properties of human amylin (insolubility, tendency to self-aggregate) have been overcome by replacement of the three amino acid residues with prolines

Ratner *et al.* (*Diabetes Technol. Ther.* 4: 51-61, 2002) provide a similar teaching (see paragraph bridging the two columns on page 52):

Native human amylin is not ideal for clinical use because of the peptide's poor solubility and propensity to aggregate.

Thus, for the reasons delineated above and due to the lack of specific direction or guidance within the instant specification, the breadth of the claims, the absence of working examples enabling the full scope, the art-recognized unpredictability factor, and the quantity of the experimentation necessary, a considerable amount of non-routine undue experimentation would have been required to reproducibly practice the full scope of the invention, as claimed. Instant claims do not meet the scope of enablement provisions of 35 U.S.C. § 112, first paragraph.

Rejection(s) under 35 U.S.C § 112, First Paragraph (New Matter)

(B) Claims 1, 7, 14 and 16 and the dependent claims 2-6, 9-13, 15 and 17 are rejected under 35 U.S.C § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

Claims 1 and 7, as amended, include the new limitations: ‘an amount effective to inhibit weight gain or induce weight loss ... of a composition comprising an amylin or amylin agonist wherein said subject is in need of treatment of obesity’. Claim 16, as amended, includes the new limitations: an amount ‘effective to inhibit weight gain or induce weight loss ... of a composition consisting essentially of an amylin or amylin agonist said subject is in need of treatment of obesity’. Claim 14, as amended, includes the new limitation: ‘salts thereof in an amount effective to treat obesity ‘in said subject by inhibiting weight gain or inducing weight loss wherein said subject is in need of treatment for obesity’. As claimed currently, ‘an amount effective to inhibit weight gain or induce weight loss in said human subject’ is not the amount of the recited amylin or the amylin agonist, but of the composition that ‘comprises’ therein an amylin, amylin agonist, or an amylin agonist analogue plus a pharmaceutically acceptable carrier plus any other element that is comprised within the composition. Applicants state that the amendment to claims 1, 7, 14 and 16 find support at page 9, lines 9-11 and 15-16, and page 22, lines 27-28 of the specification. However, lines 9-11 and 15-16 of page 9 of the specification are not supportive of ‘an amount effective to inhibit weight gain in said human subject’ or ‘an amount of a composition comprising a pharmaceutically acceptable carrier and an amylin or an amylin agonist effective to inhibit weight gain or induce weight loss in said human subject’. The description at

lines 27 and 28 of page 22 of the specification is limited to therapeutically effective amounts of amylin or amylin agonist analogue for use in the control of obesity, which are described as those that *decrease body weight*. An 'amount effective to inhibit weight gain' is an amount effective in maintaining the body weight as it existed prior to the treatment, for which there is no support. The specification does not support the new limitation of an amount of an amylin or an amylin agonist 'effective to inhibit weight gain' in a human subject in need of treatment for obesity, or 'an amount of a composition comprising a pharmaceutically acceptable carrier and an amylin or an amylin agonist effective to inhibit weight gain or induce weight loss in said human subject'. The limitation 'composition comprising' in the instant claim(s) does not exclude additional, unrecited elements. See MPEP 2111.03 [R-1]. See *Moleculon Research Corp. v. CBS, Inc.*, 793 F.2d 1261, 229 USPQ 805 (Fed. Cir. 1986); *In re Baxter*, 656 F.2d 679, 686, 210 USPQ 795, 803 (CCPA 1981); *Ex parte Davis*, 80 USPQ 448, 450 (Bd. App. 1948) ('comprising' leaves 'the claim open for the inclusion of unspecified ingredients even in major amounts') [Emphasis added]. Instead, the limitation 'comprising' allows the inclusion of additional anti-obesity agents such as exendin, CCK etc., as well as elements such as insulin or glucagon, to be present in the recited composition. Therefore, an amount of a composition 'comprising' amylin or amylin agonist would include an amount of exendin, CCK, or insulin etc. There is no descriptive support for 'an amount of a composition comprising an amylin or amylin agonist' said 'amount effective to inhibit weight gain or weight loss' in said human subject. Instead, what is supported in Example 1 and Table I is an amount of the amylin agonist analogue pramlintide (e.g., 60 micrograms QID or TID) that is effective to decrease body weight.

Additionally, there is lack of descriptive support for an amount of a 'salt' of amylin or an amylin agonist compound and its administration to a human subject in need of treatment for obesity wherein the amount of the salt is effective to treat obesity in said subject by inhibiting weight gain or inducing weight loss, wherein the salt compound is not administered in conjunction with another obesity relief agent, as claimed currently in the amended claim 14.

Furthermore, the amended claim 1 continues to include the limitation: 'method of treating obesity consisting of administering an amount effective to inhibit weight gain or induce weight loss of composition comprising an amylin or an amylin agonist and a

pharmaceutically acceptable carrier'. A method of treatment of obesity 'consisting of' such an administration step *excludes*, for example, simultaneous insulin administration, or insulin administration minutes or hours before or after the administration. However, neither the original six claims, nor the description of the methods of treatment of the instant invention support such a method of treating obesity 'consisting of' administering an effective composition comprising an amylin or an amylin agonist and a pharmaceutically acceptable carrier. For example, the originally filed specification at lines 6-8 of page 9 of the specification states [Emphasis added]:

The present invention is directed to novel methods for treating or preventing obesity in humans *comprising* the administration of an amylin or an amylin agonist, the amylin agonist analogue^{25,28,29} Pro-human amylin.

Pages 30-31 and Table I of the specification describe a statistically significant reduction in the mean baseline weight seen after the subcutaneous administration of 60 micrograms TID or 60 micrograms QID of one specific amylin agonist analogue species, pramlintide, to type II diabetic subjects for four weeks, wherein said pramlintide administration was accompanied *with the continued administration of insulin*. Thus, the method of treatment of obesity as described in the originally filed specification *comprised* insulin administration *and* the administration of a specific dose of pramlintide to type II diabetic patients. This however does not provide descriptive support for the now claimed method of treating obesity in a human in need of treatment for obesity, said method 'consisting' of administering to said subject an amount of a composition as recited comprising an amylin or any amylin agonist and a pharmaceutically acceptable carrier, wherein said amount of the composition is effective to inhibit weight gain or induce weight loss in said subject. Therefore, the above-identified limitations in the claims are considered to be new matter. *In re Rasmussen*, 650 F.2d 1212 (CCPA, 1981). New matter includes not only the addition of wholly unsupported subject matter but also, adding specific percentages or compounds after a broader original disclosure, or even omission of a step from a method. See M.P.E.P. 608.04 to 608.04(c). Applicants are to specifically point out the support for any amendments made to the disclosure. See MPEP 714.02 and 2163.06.

Rejection(s) under 35 U.S.C § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

- (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
- (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
- (c) the invention was described in-
 - (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that a patent shall not be deemed filed in the United States for the purposes of this subsection based on the filing of an international application filed under the treaty defined in section 351(a).

(C) Claims 1-7, 9-14, 16 and 17 are rejected under 35 U.S.C § 102(a) as being anticipated by Kolterman *et al.* (WO 96/40220) ('220) as evidenced by Tsanev (*Vutr. Boles* 23: 12-17, 1984, abstract).

Kolterman *et al.* ('220) taught a method of administering to insulin-taking type II diabetic human subjects a dose of 10, 30, 50, 60 or 150 micrograms per day (i.e., the amount falling in the range recited in the instant claims) of the amylin agonist composition, pramlintide or ^{25, 28, 29}pro-h-amylin, also known as AC137 (i.e., SEQ ID NO: 1), i.e., the same amylin agonist administered in the instantly claimed method. The composition consists of pramlintide and a pharmaceutically acceptable carrier, and is administered in single or multiple doses, for example, of about 30 micrograms QID, or about 60 micrograms TID or QID, i.e., an amount effective to inhibit weight gain or induce weight loss. See pages 9-11; paragraph bridging pages 20 and 21; page 21; first paragraph on page 19; lines 8-10 on page 19; and the first row reciting 'Insulin-Treated Patients' in each Table of Kolterman *et al.* ('220). Pramlintide is administered subcutaneously 1-4 times a day, before meals. See pages 9 and 22. Kolterman *et al.* ('220) additionally taught that the presence of obesity is a characteristic of 'most patients with Type II diabetes mellitus'. See page 10. Kolterman *et al.* ('220) taught the benefit of obtaining weight loss in Type II diabetic patients by teaching that hyperglycemia associated with Type II diabetes can be reversed or ameliorated by *weight loss* sufficient to restore the sensitivity of the peripheral tissues to insulin (see pages 7, first paragraph), thus teaching that Type II diabetic patients are indeed in need of weight loss or treatment of obesity. Thus, the very active step of the instantly claimed method was disclosed and practiced by Kolterman *et al.* ('220) in 1996 in the very same patient population, i.e., a human type II diabetes mellitus patients used by Applicants in Example 1 of the instant application. The prior art method is the *same* as the instantly claimed method with regard to the amylin agonist or the amylin agonist analogue, the amylin agonist composition, or the amylin agonist analogue composition (pramlintide) administered, and the

insulin-taking Type II diabetic patients used (80-90% of Type II diabetic patients being known in the art to be intrinsically obese as taught by Tsanev - see Tsanev's abstract), the subcutaneous route of the administration used, the dose and the daily frequency of the amylin agonist pramlintide administered, and the administration step prior to meals. Given Tsanev's express disclosure that 80 to 90% of type II diabetic patients are intrinsically obese, and given Kolterman's ('220) recognition that obesity is an intrinsic characteristic of most patients with Type II diabetes mellitus and the indication that these patients are in need of weight loss, Kolterman's ('220) method of subcutaneous administration of pramlintide to Type II diabetic patients in an amount that falls within the range recited in the instant claims, necessarily serves as the claimed method of treating obesity, and therefore anticipates the instantly claimed method. Since 80-90% of Type II diabetic patients are known in the art to be intrinsically obese, 80-90% of Kolterman's ('220) type II diabetic patients to whom pramlintide composition is administered, necessarily qualify as human subjects in need of treatment of obesity as recited in the instant claims. Since the structural limitations of the instantly claimed method and all of the criteria required by the instant claims are met by the teachings of Kolterman *et al.* ('220), Kolterman's ('220) method is expected to serve necessarily as the instantly claimed method and is expected to bring about the obesity-treating effect, weight gain inhibiting effect, or weight loss-inducing effect. The Office's position that Kolterman's ('220) method is the same as the Applicants' claimed method is based upon the fact that the method step, the pramlintide compound administered, the amount of the compound administered, the route by which the compound is administered, and the intrinsically obese diabetic human patients to which the pramlintide compound is administered, are the *same* in the two methods. The art-recognized intrinsic obesity being prevalent in 80 to 90% of diabetic patients as disclosed by Tsanev (see Tsanev's abstract), Kolterman's ('220) method of administration of the above-identified therapeutically effective amount (i.e., about 30 micrograms QID, or about 60 micrograms TID or QID, or a dose of 10, 30, 50, 60 or 150 micrograms per day) of the amylin agonist^{25,28,29} Pro-human amylin to intrinsically obese type 2 diabetic human subject species anticipates the instant claims. Given that the method step of the Kolterman's ('220) method and the instant claims are the same, Kolterman's ('220) method is expected to bring about weight gain-inhibiting or weight loss-causing therapeutic effect in the intrinsically obese pramlintide-treated type II diabetic patients.

Since the prior art clearly teaches the instantly claimed method, any assertions of specific functional properties attributed to the amylin agonist pramlintide in the claimed method are merely inherent and do not necessarily make the claimed method patentable. The art-recognized intrinsic obesity being prevalent in as much as 80 to 90% of diabetic patients as disclosed by Tsanev (see abstract), Kolterman's ('220) method of administration of the above-identified therapeutically effective amount (i.e., about 30 micrograms QID, or about 60 micrograms TID or QID, or a dose of 10, 30, 50, 60 or 150 micrograms per day) of the amylin agonist^{25,28,29} Pro-human amylin to intrinsically obese type 2 diabetic human subject species anticipates the instant claims.

Claims 1-7, 9-14, 16 and 17 are anticipated by Kolterman *et al.* ('220). The publication of Tsanev is **not** used as a secondary reference in combination with the reference of Kolterman *et al.* ('220), but rather is used to show that every element of the claimed subject matter is disclosed by Kolterman *et al.* ('220), with the unrecited limitation(s) being inherent as evidenced by the state of the art. See *In re Samour* 197 USPQ 1 (CCPA 1978). Tsanev's extrinsic evidence makes clear that the missing descriptive matter, i.e., 80 to 90% prevalence of obesity in Kolterman's ('220) diabetic subjects administered with pramlintide, is necessarily present in the method thing described by Kolterman *et al.* ('220). The method of Kolterman *et al.* ('220) clearly anticipates the claimed method of the instant invention, because Kolterman *et al.* ('220) taught the very step of the instantly claimed method in the very same type II diabetic human patient population. Since the structural limitations of the instantly claimed method and *all* of the criteria required by the instant claims are met by the disclosure of Kolterman *et al.* ('220), Kolterman's ('220) method is expected to serve necessarily as the instantly claimed method and is expected to bring about the weight gain-inhibiting effect, weight loss-inducing effect, or obesity-treating effect.

(D) Claims 1-7, 9, 11-14, 16 and 17 are rejected under 35 U.S.C § 102(b) as being anticipated by Kolterman *et al.* (*Diabetologia* 39: 492-499, April, 1996) (Kolterman *et al.*, 1996) as evidenced by Itasaka *et al.* (*Psychiatr. Clin. Neurosci.* 54: 340-341, June 2000).

It is noted that the human patient in need of the recited treatment according to the instant invention is expressly identified in the instant specification as one having a body weight of 79 kg. A 70 kg patient is not excluded from the scope of the instant invention 'as a human subject in

need thereof', but is expressly included. The recited therapeutic amount range of 'about 0.1 milligrams per day to about 1 milligram per day', or 'about 0.01 to about 5 mg/day', or 0.03 to about 5 mg/day of the amylin agonist or amylin agonist analogue, pramlintide, administered is specifically "for a 70 kg patient". See lines 4-8 of page 23 of the substitute specification; and paragraph bridging pages 23 and 24 and lines 3-7 on page 24 of Applicants' response filed December 2002.

Kolterman *et al.* (1996) taught a method of subcutaneous administration of 30, 100, or 300 μ g of pramlintide composition or AC137 (i.e., ^{25,28,29}pro-h-amylin or SEQ ID NO: 1), a human amylin analogue, to human patients with insulin-dependent diabetes mellitus or IDDM who are on insulin. Pramlintide is administered three times daily for a period of 14 days. See abstract; and page 493. The mean body weight \pm SEM of diabetic patients included in Kolterman's (1996) method who were administered subcutaneously with 30 micrograms, 100 micrograms, and 300 micrograms of pramlintide, three times a day for 14 days, was 70.6 ± 2.7 , 74.4 ± 2.5 , and 75.7 ± 2.6 respectively. Therefore, the 70.6 to 75.7 kg insulin-taking diabetic patients from Kolterman's (1996) study qualify as human subjects in need of treatment for obesity as recited in the instant claims. Additionally, even BMI-wise, Kolterman's (1996) diabetic subjects meet the limitation 'a human subject in need of treatment for obesity' as recited in the instant claims, because the diabetic subjects included in Kolterman's method (1996) had a BMI of up to 27. See second full paragraph under 'Subjects, materials and methods'. Therefore, Kolterman's (1996) diabetic subjects having a BMI at least in the range of 24 up to 27 do qualify as diabetic subjects in need of treatment for obesity in light of what is known in the art. For example, Itasaka *et al.* teach that a BMI of 24.0 to 26.4 represents mild obesity and 26.4 and heavier (i.e., including a BMI of 26.4 to 27) represents obesity in humans (see abstract of Itasaka *et al.*). Kolterman's (1996) pramlintide composition did not comprise another obesity relief agent, but consisted of or consisted essentially of pramlintide. The pramlintide composition was injected subcutaneously to the human patients (see 'Study design') and therefore is expected to inherently contain a pharmaceutically acceptable carrier therein. The amount administered was 30 micrograms three times a day to 'about 0.1 milligrams' or 300 micrograms per day. See 'Study design'; Table 1; and paragraph there below. Kolterman's (1996) subcutaneous administration of the above-identified therapeutically effective amount of the amylin agonist, pramlintide or SEQ ID NO: 1, to diabetic human subjects taking insulin and weighing 70 kg or more, or having a BMI falling in the BMI range of 24 up to 27,

necessarily serves as the Appellants' method of treating obesity by inhibiting weight gain or inducing weight loss in the human subject genus, as claimed currently, and therefore anticipates the instant claims. Thus, the very active step recited in the instantly claimed method was disclosed and practiced by Kolterman *et al.* in April, 1996. Given that the method step in Kolterman's (1996) method and the instant claims are the *same*, and the amylin agonist analogue pramlintide administered and its amount administered are the *same*, Kolterman's (1996) method is expected to necessarily bring about the same weight gain-inhibiting (i.e., maintaining of existing body weight) or weight loss-inducing therapeutic effect in Kolterman's (1996) pramlintide-treated diabetic patients who are on insulin. Since the prior art clearly teaches the claimed method, any assertions of specific functional properties attributed to the amylin agonist pramlintide administered in the claimed method are merely inherent and do not necessarily make the claimed method patentable.

Claims 1-7, 9, 11-14, 16 and 17 are anticipated by Kolterman *et al.* (1996). The publication of Itasaka *et al.* is **not** used as a secondary reference in combination with the reference of Kolterman *et al.* (1996), but rather is used to show that every element of the claimed subject matter is disclosed by Kolterman *et al.* (1996) with the unrecited limitation(s) being inherent as evidenced by the state of the art. See *In re Samour* 197 USPQ 1 (CCPA 1978). Itasaka's extrinsic evidence makes clear that the missing descriptive matter, i.e., prevalence of obesity in 80 to 90% Kolterman's (1996) insulin-taking diabetic subjects administered with ^{25,28,29}Pro-human amylin, is necessarily present in the method thing described by Kolterman *et al.* (1996). The method of Kolterman *et al.* (1996) clearly anticipates the claimed method of the instant invention, because Kolterman *et al.* (1996) taught the very step of the instantly claimed method in diabetic human patients.

(E) Claims 7, 14 and 16 are rejected under 35 U.S.C § 102(e)(2) as being anticipated by Beumont *et al.* (US 5,321,008) ('008) as evidenced by Tsanev (*Vutr. Boles* 23: 12-17, 1984, abstract).

The applied reference has a common assignee with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 102(e) might be overcome either by a showing under 37 C.F.R. 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not the invention 'by another', or by an appropriate showing under 37 C.F.R. 1.131.

It is noted that the limitation in the instant claim 16: 'a composition consisting essentially of an amylin or an amylin agonist', and the limitation in claim 14: 'method ... comprising wherein said compound is not administered in conjunction with another obesity relief agent', do not exclude the administration of an anti-diabetic agent, insulin, glucagon, a gastric emptying-inhibiting agent such as exendin etc. It is further noted that 'amylin agonist' is defined in the instant specification as a peptide or non-peptide compound that mimics the effect of amylin. See paragraph bridging pages 13 and 14 of the originally filed specification. Calcitonin and CGRP are described in the instant specification as sharing the food intake-suppressing action/effect of peripherally or centrally administered amylin. See paragraph bridging pages 9 and 10 of the originally filed specification.

Beumont *et al.* ('008) taught a method of subcutaneous administration to insulin-requiring humans who suffer from Type 1 or Type 2 diabetes mellitus a therapeutically effective amount of an amylin agonist *alone* such as calcitonin, or calcitonin and insulin, contained in a pharmaceutically acceptable carrier. See claims 11, 7, 13 and 4; lines 14-17 in column 5; lines 8-11 and 49-54 in column 12; and lines 34 and 35 in column 2. Claim 11 of the '008 patent is directed to the method of administering a therapeutically effective amount of the amylin agonist calcitonin to insulin-requiring humans with diabetes mellitus. The 'therapeutically effective amount' taught by Beumont *et al.* ('008) includes the typical dosage units of about 0.1 to 1 mg of calcitonin. See first full paragraph in column 13. The amount effective to treat obesity, the amount effective to inhibit weight gain, or the amount effective to induce weight loss encompassed in the instant claims as described in the instant application of about 0.01 milligrams to about 5 milligrams per day, about 0.05 milligrams to about 2 milligrams per day, or 300 micrograms per dose, falls within the range of the therapeutically effective amount disclosed in the '008 patent. Given the art-known prevalence of intrinsic obesity in 80% to 90% of diabetic patients as disclosed by Tsanev (see abstract), 80 to 90% of diabetic patients used in the method disclosed in the '008 patent qualify as human patients in need of treatment for obesity. Therefore, the method of the '008 patent comprising the administration of about 0.1 to 1 mg of calcitonin to diabetic human species anticipates the instant claims. Given that the method step of the '008 patent and the instant claims is the same, and the amylin agonist administered and the amount administered are the same as the ones described in the instant specification, the method of the '008 patent is expected to bring about a obesity-treating effect, weight gain-inhibiting effect, or weight loss-inducing effect in Beumont's intrinsically obese, calcitonin-treated diabetic patients as defined in the instant invention.

Since the structural limitations of the instantly claimed method and *all* of the criteria required by the instant claims are met by the teachings of the '008 patent, Beumont's ('008) method is expected to serve necessarily as the instantly claimed method and is expected to bring about the obesity-treating effect, weight gain inhibiting effect, or weight loss-inducing effect. The Office's position that Beumont's ('008) method is the same as the Applicants' claimed method is based upon the fact that the method step, the amylin agonist calcitonin administered and its amount administered, the subcutaneous route by which the amylin agonist is administered, and the intrinsically obese diabetic human patient species to which the amylin agonist is administered, are the *same* in the two methods. The art-recognized intrinsic obesity being prevalent in 80 to 90% of diabetic patients as disclosed by Tsanev (see abstract), Beumont's ('008) method of administration of the above-identified therapeutically effective amount (i.e., dosage units of about 0.1 to 1 mg) of the amylin agonist calcitonin to 80 to 90% of intrinsically obese type 2 diabetic human subject species anticipates the instant claims. Given that the method step of the Beumont's ('008) method and the instant claims are the same, Beumont's ('008) method is expected to bring about the weight gain-inhibiting, weight loss-causing or obesity-treating effect in the intrinsically obese calcitonin-treated insulin-requiring human diabetic patients of the '008 patent. Since the prior art clearly teaches the instantly claimed method, any assertions of specific functional properties attributed to the amylin agonist, calcitonin, in the claimed method are merely inherent and do not necessarily make the claimed method patentable.

Claims 7, 14 and 16 are clearly anticipated by Beumont *et al.* ('008). The publication of Tsanev is **not** used as a secondary reference in combination with the reference of Beumont *et al.* ('008), but rather is used to show that every element of the claimed subject matter is disclosed by Beumont *et al.* ('008) with the unrecited limitation(s) being inherent as evidenced by the state of the art. See *In re Samour* 197 USPQ 1 (CCPA 1978). Tsanev's extrinsic evidence makes clear that the missing descriptive matter, i.e., prevalence of obesity in 80 to 90% of Beumont's ('008) insulin-requiring diabetic subjects administered with calcitonin, is necessarily present in the method thing described by Beumont *et al.* ('008). The method of Beumont *et al.* ('008) clearly anticipates the claimed method of the instant invention, because Beumont *et al.* ('008) taught the very step of the instantly claimed method in the very same diabetic human patient species.

(F) Claims 7, 14, 16 and 17 are rejected under 35 U.S.C § 102(e)(2) as being anticipated by Gaeta *et al.* (US 5,686,411) ('411) as evidenced by Tsanev (*Vutr. Boles* 23: 12-17, 1984, abstract).

The applied reference has a common assignee with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 102(e) might be overcome either by a showing under 37 C.F.R. 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not the invention 'by another', or by an appropriate showing under 37 C.F.R. 1.131.

The limitation 'consisting essentially of' in the instant claim 16 and the limitation 'method ... comprising wherein said compound is not administered in conjunction with another obesity relief agent' in claim 14 are interpreted as not excluding the presence of an anti-diabetic agent, insulin, glucagon, a gastric emptying-inhibiting agent etc. in the recited composition.

Gaeta *et al.* ('411) taught a method of administering to mammals having diabetes mellitus, including patients seen by a medical practitioner, i.e., humans, a therapeutically effective amount of the amylin agonist of claim 19, ^{25,28,29}Pro-human amylin (SEQ ID NO: 1 or pramlintide). See claims 34, 35 and 19; and lines 45-53 in column 7 of the '411 patent. Gaeta *et al.* ('411) taught the 'therapeutically effective amount' of the amylin agonist to include the dosage units of 0.1 to 5 mg or 0.5 to 1.0 mg of the amylin agonist. See lines 53-59 in column 8. The amount effective to treat obesity, inhibit weight gain, or induce weight loss encompassed in the instant claims as described in the instant application, for example, about 0.01 milligrams to about 5 milligrams per day, about 0.05 milligrams to about 2 milligrams per day, or 300 micrograms per dose, falls within the range of therapeutically effective amount of the amylin agonist disclosed in the '411 patent. Lines 9-14 of column 3 of the '411 patent describe that the limitation 'diabetes mellitus' includes *insulin-requiring* diabetes mellitus and that the administration is of amylin agonist analogue *alone*. The amylin agonist composition comprises a pharmaceutical carrier and the amylin agonist without insulin or glucagon. See lines 9-11 in column 7 and lines 37-39 in column 8. Given the art-known prevalence of intrinsic obesity in 80% to 90% of diabetic patients as disclosed by Tsanev (see abstract), 80% to 90% of the diabetic patients administered with the amylin agonist ^{25,28,29}Pro-human amylin in the method disclosed by the '411 patent qualify as a human patient in need of treatment for obesity. Therefore, the method of the '411 patent comprising the administration of 0.1 to 5 mg, or 0.5 to 1.0 mg of the amylin agonist ^{25,28,29}Pro-human amylin to diabetic

humans anticipates the instant claims. Given that the method step of the '411 patent and the instant claims are the same, the amylin agonist, ^{25,28,29}Pro-human amylin, administered and the amount administered are the same, the structural limitations of the instantly claimed method and *all* of the criteria required by the instant claims are met by the teachings of the '411 patent. Gaeta's ('411) method is expected to serve necessarily as the instantly claimed method and is expected to bring about a therapeutic effect, weight gain-inhibiting effect, and weight loss-inducing effect in the intrinsically obese ^{25,28,29}Pro-human amylin-treated insulin-requiring diabetic patients of Gaeta ('411). The Office's position that Gaeta's ('411) method is the same as the Appellants' claimed method is based upon the fact that the method step, the amylin agonist, ^{25,28,29}Pro-human amylin administered, the amount of the ^{25,28,29}Pro-human amylin administered, and the one intrinsically obese diabetic human patients to whom the ^{25,28,29}Pro-human amylin is administered, are the *same* in the two methods. The art-recognized intrinsic obesity being prevalent in 80 to 90% of diabetic patients as disclosed by Tsanev (see abstract), Gaeta's ('411) method of administration of the above-identified therapeutically effective amount (i.e., 0.1 to 5 mg, or 0.5 to 1.0 mg) of the amylin agonist ^{25,28,29}Pro-human amylin to intrinsically obese type 2 diabetic human subject species anticipates the instant claims. Since the prior art clearly teaches the instantly claimed method, any assertions of specific functional properties attributed to the amylin agonist ^{25,28,29}Pro-human amylin used in the claimed method are merely inherent and do not necessarily make the claimed method patentable.

Claims 7, 14 and 16 are clearly anticipated by Gaeta *et al.* ('411). The publication of Tsanev is **not** used as a secondary reference in combination with the reference of Gaeta *et al.* ('411), but rather is used to show that every element of the claimed subject matter is disclosed by Gaeta *et al.* ('411) with the unrecited limitation(s) being inherent as evidenced by the state of the art. See *In re Samour* 197 USPQ 1 (CCPA 1978). Tsanev's extrinsic evidence makes clear that the missing descriptive matter, i.e., the prevalence of obesity in 80 to 90% of Gaeta's ('411) insulin-requiring diabetic subjects administered with ^{25,28,29}Pro-human amylin, is necessarily present in the method thing described by Gaeta *et al.* ('411). The method of Gaeta *et al.* ('411) clearly anticipates the claimed method of the instant invention, because Gaeta *et al.* ('411) taught the very step of the instantly claimed method in the very same diabetic human patient species.

Double Patenting Rejections

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970) and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 C.F.R. 1.321(c) may be used to overcome an actual or provisional rejection based on a non-statutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 C.F.R. 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 C.F.R. 3.73(b).

(G) Claims 7, 14, 16 and 17 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 34 and 35 of the US patent 5,686,411 issued to Gaeta *et al.* ('411) as evidenced by Tsanev (*Vutr. Boles* 23: 12-17, 1984, abstract).

The method of treatment claimed in claims 34 and 35 of the '411 patent includes administering to a mammal with diabetes mellitus a therapeutically effective amount of the amylin agonist of claim 19, ^{25,28,29}Pro-human amylin (SEQ ID NO: 1 or pramlintide). The portion of the disclosure of the '411 patent at lines 45-53 in column 7 supporting the limitation 'mammal' does not exclude, but expressly includes a patient seen by a medical practitioner, i.e., humans. The portion of the disclosure of the '411 patent at second paragraph under 'Summary of the Invention' supporting the limitations 'diabetes mellitus' and 'administration of an amylin agonist analogue' include *insulin-requiring* diabetes mellitus and administration of an amylin agonist analogue alone (i.e., consisting of) or in conjunction with (comprising or consisting essentially of) insulin or a glucagon, i.e., not in conjunction with another obesity relief agent. The portion of the disclosure of the '411 patent at lines 53-59 in column 8 supporting the limitation 'therapeutically effective amount' of the amylin agonist includes the dosage units of 0.1 to 5 mg or 0.5 to 1.0 mg of the amylin agonist. The amount effective to induce weight loss, i.e., treat obesity, encompassed in the instant claims as described in the instant application of about 0.01 milligrams to about 5 milligrams

per day, about 0.05 milligrams to about 2 milligrams per day, about 0.1 milligrams to about 1 milligram per day, or 300 micrograms per dose, falls within the range disclosed in the '411 patent. Given the art-known prevalence of intrinsic obesity in 80% to 90% of diabetic patients as disclosed by Tsanev, 80% to 90% of the human diabetic patients used in the method disclosed in the '411 patent qualifies as human patients in need of treatment for obesity. Therefore, the method of the '411 patent comprising or consisting of the administration of 0.1 to 5 mg, or 0.5 to 1.0 mg of the amylin agonist,^{25,28,29} Pro-human amylin alone or in conjunction with insulin or glucagon, to diabetic human species anticipates the instant claims. Given that the method step of the '411 patent and the instant claims are the same, the amylin agonist analogue pramlintide used and its amount administered are the same, and the human diabetic patient used is the same, the method of the '411 patent is expected to bring about a weight gain-inhibiting effect, weight loss-inducing effect, or obesity-treating effect in the intrinsically obesity diabetic patient species administered with a therapeutically effective amount of the pramlintide as claimed in the instant invention. Since the structural limitations of the instantly claimed method and *all* of the criteria required by the instant claims are met by the disclosure of Gaeta *et al.* ('411), Gaeta's ('411) method is expected to serve necessarily as the instantly claimed method and is expected to bring about the weight gain-inhibiting effect, weight loss-inducing effect, or obesity-treating effect.

(H) Claims 7, 14 and 16 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 11 and 13 of US patent 5,321,008 issued to Beumont *et al.* ('008) as evidenced by Tsanev (*Vutr. Boles* 23: 12-17, 1984, abstract).

The method of treatment claimed in claims 11 and 13 of the '008 patent includes administering to a human with type 2 diabetes mellitus a therapeutically effective amount of the amylin agonist, calcitonin. The portion of the disclosure of the '008 patent at lines 14-17 in column 5; lines 8-11 and 49-54 in column 12; and lines 34 and 35 in column 2 that supports the claims includes subcutaneous administration to an insulin-requiring human who suffers from Type 1 or Type 2 diabetes mellitus a therapeutically effective amount of an amylin agonist *alone* such as calcitonin (i.e., consisting of), or calcitonin and insulin (i.e., comprising or consisting essentially of), contained in a pharmaceutically acceptable carrier. The portion of the disclosure of the '008 patent at first full paragraph in column 13 of the '008 patent supporting the 'therapeutically effective amount' includes the typical dosage units of about 0.1 to 1 mg of calcitonin. The amount effective to treat obesity, or the amount effective to induce

weight loss encompassed in the instant claims as described in the instant application, for example, about 0.01 milligrams to about 5 milligrams per day, about 0.05 milligrams to about 2 milligrams per day, or 300 micrograms per dose, falls within the range of the therapeutically effective amount disclosed in the '008 patent. Given the art-known prevalence of intrinsic obesity in 80% to 90% of diabetic patients as disclosed by Tsanev (see abstract), 80 to 90% of *insulin-requiring* human diabetic patients used in the method in the above-identified of the '008 patent qualify as human patients in need of treatment for obesity. Therefore, the method of the '008 patent comprising the administration of about 0.1 to 1 mg of calcitonin to insulin-requiring diabetic human species anticipates the instant claims. Given that the method step of the '008 patent and the instant claims is the same, and the amylin agonist calcitonin administered and the amount administered are the same, and the human diabetic patient species to whom calcitonin is administered is the same as the one described in the instant application, the method claimed in the '008 patent is expected to bring about an obesity-treating effect, weight gain-inhibiting effect, or weight loss-inducing effect in the intrinsically obese calcitonin-treated diabetic patient species of the '008 patent. Since the structural limitations of the instantly claimed method and *all* of the criteria required by the instant claims are met by the teachings of the '008 patent, Beumont's ('008) method is expected to serve necessarily as the instantly claimed method and is expected to bring about the obesity-treating effect, weight gain-inhibiting effect, or weight loss-inducing effect. The art-recognized intrinsic obesity being prevalent in 80 to 90% of diabetic patients as disclosed by Tsanev (see abstract), Beumont's ('008) method of administration of the above-identified therapeutically effective amount (i.e., dosage units of about 0.1 to 1 mg) of the amylin agonist of calcitonin to 80 to 90% of intrinsically obese type 2 diabetic human subject species anticipates the instant claims.

(10) Response to Appellants' Arguments

(I) In response to the rejection of claims 1-7 and 9-17 made in paragraph 29 of the Office Action mailed 02/11/08 and maintained in paragraph 14 of the Office Action mailed 04/30/08 under 35 U.S.C § 112, first paragraph, as being non-enabled with regard to the full scope, Appellants submit the following **arguments**.

(a) The proper standard for determining compliance with the enablement requirement is whether the specification provides sufficient information to permit one skilled in the art to make and use the claimed invention. *United States v. Telectronics, Inc.*, 8 USPQ2d 1217, 1223 (Fed. Cir. 1988). The test

of enablement is not whether experimentation is necessary, but rather whether any experimentation that is necessary is undue. A considerable amount of experimentation is permitted, provided that it is merely routine, or provided that the specification provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed. *In re Wands*, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). A specification that discloses how to make and use a claimed invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented "must be taken as in compliance with the enabling requirement of the first paragraph of § 112 unless there is reason to doubt the objective truth of the statements contained therein." *In re Brana*, 51 F.3d 1560, 1566, 34 U.S.P.Q.2d 1436, 1441 (Fed. Cir. 1995) (quoting *In re Marzocchi*, 439 F.2d 220, 223, 169 U.S.P.Q. 367, 369 (C.C.P.A. 1971).

(b) Regarding the quantity of experimentation needed, the standard for determining enablement is whether the experimentation needed to practice the invention is undue or unreasonable. *Mineral Separation v. Hyde*, 242 U.S. 261, 270 (1916). One of ordinary in them would have the ability to select amylin and amylin agonist peptides for use in the claimed methods without undue experimentation in view of the specification. Methods of synthesis of a defined group of compositions useful in the claimed methods are provided or known in the art, as are methods of administration and methods of weight determination.

(c) Regarding the amount of direction or guidance presented, the specification *broadly* discloses that the claimed amylin or amylin agonist compounds are useful in the treatment of obesity in a subject in need thereof. There is express guidance as to modes of administration, therapeutic dosages, mechanisms for assessing therapeutic efficacy, as well as a working example to demonstrate the statistically significant ability of an exemplary amylin compound to treat obesity in a human subject in need thereof. In the working example, the human subjects were Type 2 diabetics. The working example illustrated Type 2 diabetic subjects taking insulin does not render the scope of enablement limited to this subject population. Rather, it demonstrates that in a particularly difficult to treat, obese subject population (Type 2 diabetic subjects taking insulin), an exemplary amylin compound is therapeutically effective in the treatment of obesity. Taken together with the teachings of the specification (e.g., page 18, paragraph 3 to page 23, paragraph 2), the working example provides a base-line approach for establishing therapeutic efficacy of exemplary amylin compounds within the context of the presently

claimed methods. Utilizing similar study structures, Appellants have in fact established that exemplary amylin compounds are effective in the treatment of obesity in non-diabetic subjects as well (see, e.g., IDS entries AZ1, AZ2, AZ4 and AZ5 of Aronne, et al. and Smith, et al. of record). This evidence confirms the teachings of the specification, and demonstrates that Appellants' working example in fact provides enablement of the efficacy of a particularly difficult to treat, chronically obese subject population.

(d) The Office is impermissibly attempting to limit the scope of enablement to the scope of the working examples. Based on the extensive guidance provided in the specification, including the human clinical study results, as well as the high level of skill in the art, the skilled artisan would be able to evaluate efficacy of amylin compounds in accordance with the methods of the inventions to ascertain therapeutically effective amounts of the recited amylin compounds. The Office's characterization of Example 1 only serves to underscore the enablement of the claims in this regard. Example 1 describes a clinical study wherein routine dosages were evaluated in human clinical subjects to ascertain a therapeutically effective dose as well as effective administration regimens. The working examples, in combination with the disclosure of the specification and knowledge of one skilled in the art, amply enable the full scope of the invention as presently claimed.

(e) With respect to reasons for doubting the objective truth of the specification based on Rink's disclosure as relied upon by Appellants' prior admission in their Appeal Brief filed July 2000, when read in context, it is clear that Rink only contemplates amylin-induced appetite suppression in rodents, not in humans. Rink does not describe the treatment of obesity in humans using amylin or an amylin agonist as required by the claims of the present invention.

(f) Regarding the nature of the invention, Appellants agree with the Office's assertion that the nature of the invention is pertinent to the treatment of obesity in a human subject in need of such treatment comprising or consisting of administering an amylin, an amylin agonist, or an amylin agonist analogue composition or compound in an amount effective to inhibit weight gain or induce weight loss in the subject. Specifically, the invention contemplates the treatment of obesity in human subject in need of treatment by the administration of an amylin or amylin agonist. Indeed, Appellants discovered that amylin or agonists thereof can be used for the treatment of obesity.

(g) The relative skill of one of ordinary skill in the art to which the invention pertains is very high. Regarding the state of the prior art, Appellants agree in part with the Office's characterization of obesity or adiposity as a 'chronic disease' that is highly prevalent in modern society which is strongly associated with multiple conditions including diabetes mellitus, insulin resistance, hypertension, etc. However, the Office appears to have failed to note that *the prior art does not disclose the subject matter of the claims of the present application* taken as a whole. Indeed, it was Appellants' discovery that amylin or amylin agonists could be administered to a human subject in need of treatment for obesity. In this respect, one of ordinary skill in the art would have the ability to select amylin and amylin agonist peptides for use in the claimed methods without undue experimentation. Indeed, amylin compounds recited in the claims are generally recognized as a defined class of compounds, and the specification provides ample direction and guidance to those skilled in the art with regard to the identification of such amylin compounds useful in the context of the claimed methods.

(h) Regarding the predictability or unpredictability of the art, the Office alleges that the state of the art with regard to the use of amylin in obesity is unpredictable and that Baron *et al.* and Ratner *et al.* indicate the impracticability of using amylin as a therapeutic agent. Both Baron *et al.* and Ratner *et al.* actually support enablement of the claimed invention. Whether native human amylin is suitable for use as a commercial drug product is not a proper standard for judging the enablement of the present claims. Given the teachings of the instant specification, one of ordinary in the art would have the ability to select amylin and amylin agonist peptides for use in the claimed methods without undue experimentation. This further confirms that both amylin and amylin agonists are well known compounds that have been widely characterized. Given this, one of ordinary skill in the art would have the requisite skill to practice the invention commensurate in scope with the claims without undue experimentation.

(i) Regarding the breadth of the claims, in rejecting the claims the Office has impermissibly attempted to limit the invention to the scope of the examples. Such a standard is legally incorrect. As set forth in MPEP 3 2164.02, "[f]or a claimed genus, representative examples together with a statement applicable to the genus as a whole will ordinarily be sufficient if one skilled in the art (in view of level of skill, state of the art and the information in the specification) would expect the claimed genus could be used in that manner without undue experimentation." Tables I - II and Examples 1-8 disclose data relating to the claimed methods and exemplary amylin compounds. Alone, this disclosure is sufficient

such that one of ordinary skill in the art at the time the invention was made would have the ability to practice the invention commensurate in scope with the claims. Appellants disagree with the Office's assertion that the only amylin agonist analogue species within the recited broad genus that is being used for inducing weight loss in humans is pramlintide. Again, the Office appears to be focusing on Example 1 rather than the teachings of the specification as a whole and the level of ordinary skill in the art. In this regard, it is noted that amylin compounds recited in the claims are generally recognized as a defined class of compounds, and the specification provides ample direction and guidance to those skilled in the art with regard to the identification of such amylin compounds useful in the context of the claimed methods. Furthermore, the specification is replete with examples of amylin agonists, including functional variants, fragments, and derivatives of amylin and amylin agonists. See e.g. specification page 13 paragraph 4 to page 17, paragraph 1. Given at least the discussion in the background concerning amylin agonists, as well as the description of SEQ ID NO: 12-17, one of ordinary skill in the art having read the specification would have the ability to select known amylin agonists without undue experimentation. Moreover, to the extent that any additional experimentation may be required, the performance of routine and well known steps cannot create undue experimentation even if it is laborious. See *In re Wands* (Id.); *In re Angstadt*, 190 USPQ 214 (CCPA 1976). Given the knowledge in the art, and based on the guidance provided in the specification regarding the extensive exemplary embodiments of amylin compounds, receptor binding assays and other assays for determining amylin activity, including the soleus muscle assay, and exemplary clinical study designs, additional therapeutically active amylin agonists can be identified within the context of the present claims without the need for undue experimentation. The specification provides numerous examples of compounds within the scope of the recited genus, and guidance with regard to assays and clinical studies in the examples useful to evaluate the efficacy of the compounds in the methods of the present invention. Based on such guidance, one of skill in the art would be able to practice the claimed invention with only routine experimentation.

(j) Claim 2 requires that the amylin agonist of claim 1 is an amylin agonist analogue. As generally understood by those of skill in the art, amylin analogues are compounds that are structurally related to the reference compound, i.e., amylin. As explained in the specification and understood by those having ordinary skill in the art, *an amylin analogue can have one or more amino acid substitutions, deletions, inversions, or additions compared to a native or naturally occurring amylin.*

Furthermore, claim 2 merely requires that the amylin analogue is an amylin agonist analogue. In accordance with the claims and the knowledge of those of ordinary skill in the art, the recited amylin agonist analogues are both structurally and functionally defined. Hence, claim 2 is enabled. With regard to the Office's position on the scope of various claim terms and transitional phrases, various claim terms such as obesity and administering are discussed in a broad context. While Appellants do not necessarily agree with the exact definition provided by the Office, Appellants do acknowledge the broad scope of such terms commensurate with the present specification. With regard to the use of traditional transitional phrases such as 'comprising', 'consisting of' and 'consisting essentially of', such language has been used in the traditional context. Within the context of the claimed methods for treating obesity, such terms of art would have their traditional meanings and limitations with regard to claim elements relevant to the treatment of obesity. However, such traditional claim terms would have no bearing on components, steps, or elements outside of the claimed scope of the treatment of obesity.

The Office submits the following response to Appellants' arguments:

In the instant application, except for one amylin agonist species, pramlintide, Appellants have not established that a representative number of the vast number of exemplary amylin compounds encompassed within the scope of the claims is indeed effective in the treatment of obesity in diabetic or non-diabetic subjects. With regard to the use of amylin and non-pramlintide amylin agonists in treatment of obesity in humans, the Office agrees with Appellants that *the prior art does not disclose the subject matter of the claims of the present application*. It is because of this reason, one of skill in the art would look into Appellants' specification for specific guidance and direction to practice the full breadth of the instantly claimed method, but is lacking. A mere description of methods of synthesizing amylin agonist peptides is not sufficient to enable the full scope of the method of treating obesity as claimed. Even if a skilled artisan selected some of the exemplary amylin agonist analogues recited in the instant specification, there is no predictability that said non-pramlintide amylin agonist analogues would have the therapeutic effect against a particularly difficult to treat obese diabetic or morbidly obese human subjects and is usable in the claimed method.

With regard to Appellants' statement that an amylin analogue can have one or more amino acid substitutions, deletions, inversions, or additions compared to a native or naturally occurring amylin, it should be noted that, other than pramlintide, no amylin analogues having one or more amino acid substitutions, deletions, inversions, or additions compared to a native or naturally occurring amylin

have been shown to be effective in treating obesity and therefore usable in the methods as claimed.

How to make one or more the one substitutions, deletions, inversions, or additions in an amylin analogue in such a way that the resultant products would still have weight loss-inducing or weight gain-inhibiting, or obesity-inducing effect is neither taught by Appellants, nor is it known in the state of the art.

With regard to the quantity of experimentation needed, the standard for determining whether the specification meets the enablement requirement was cast in the Supreme Court decision of *Mineral Separation v. Hyde*, 242 U.S. 261, 270 (1916) which postured the question: 'is the experimentation needed to practice the invention undue or unreasonable'. That standard is still the one to be applied. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). In the instant case, no guidance or direction has been provided in the instant specification so that one could predict which of the amylin agonist analogue species other than pramlintide would have the requisite therapeutic effect against obesity. Because there is no way to predict *a priori* which amylin, amylin agonists, or amylin agonist analogues from the specification or from the chemical structures alone would be therapeutically active against obesity in diabetic or non-diabetic humans subjects, including morbidly obese human subjects, an extraordinary amount of trial and error experimentation is required to identify the obesity-treating amylin agonist analogue species. Assuming *arguendo* that the experimentation required is routine, and if one of skill in the art screens innumerable non-pramlintide amylin agonist species or amylin agonist analogue species currently encompassed within the recited genus, including those disclosed in Examples 2 and 3 or Table II of the instant invention, using receptor binding assays and assays for amylin activity, there is absolutely no predictability that a non-pramlintide amylin agonist having amylin activity would have a weight gain-inhibiting effect, weight loss-inducing effect, obesity-relieving effect, or food intake-reducing effect given the Applicants' admission that amylin itself has no effect on food intake. Given this and the lack of showing within the instant specification as explained above, the weight loss-inducing or weight gain-inhibiting effect of any amylin or any non-pramlintide amylin agonist analogue mimicking effect(s) of amylin, administered alone or as an adjunct to insulin therapy, to an obese diabetic or obese non-diabetic human subject, is simply not predictable. Applicants have provided no guidance with regard to the use of extraordinarily large genus of amylin, amylin agonists, and amylin agonist analogues in the treatment of obesity in humans. *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970)

states: 'The amount of guidance or direction needed to enable the invention is inversely related to the amount of knowledge in the state of the art as well as the predictability in the art'. The amount of guidance or direction refers to that information in the application, as originally filed, that teaches exactly how to make or *use* the invention. The more is known in the prior art about the nature of the invention, how to make, *and* how to use the invention, and the more predictable the art is, the less information needs to be explicitly stated in the specification. In contrast, if little is known in the prior art about the nature of the invention and the art is unpredictable, the specification would need more detail as to how to make and use the invention in order to be enabling' (MPEP 2164.03). MPEP also states that physiological activity can be considered inherently unpredictable. Whether the specification would have been enabling *as of the filing date* involves consideration of the nature of the invention, the state of the prior art, and the level of skill in the art. The initial inquiry is into the nature of the invention, i.e., the subject matter to which the claimed invention pertains. The nature of the invention becomes the backdrop to determine the state of the art and the level of skill possessed by one skilled in the art. The state of the prior art is what one skilled in the art would have known, *at the time the application was filed*, about the subject matter to which the claimed invention pertains. The relative skill of those in the art refers to the skill of those in the art in relation to the subject matter to which the claimed invention pertains *at the time the application was filed*. See MPEP § 2164.05(b). None of the post-filing references and abstracts cited by Appellants represents the state of the art *at the time of filing*. The abstracts of Aronne *et al.* (*Obesity* 14: A17, 2006) and Smith *et al.* (*Diabetes* 56: A88, 2007) submitted by Appellants are silent about the diabetic or non-diabetic status of the subjects included in the study. Both are limited to the use of the single amylin agonist analogue species, pramlintide in the method described therein. The post-filing teachings of Aronne *et al.* (*J. Endocrinol. Metabol.* 92: 2977-2983, 2007) and Smith *et al.* (*J. Am. J. Physiol. Endocrinol. Metabol.* 293: 620-627, 2007) submitted by Appellants are also limited to the use of one amylin agonist analogue species, pramlintide, for reducing caloric intake and meal size, or for reducing body weight. These two post-filing publications support the Office's position on the lack of enablement of the full scope of the instant claims by confirming that even about a decade after the effective filing date of the instant application, the only amylin agonist analogue species within the recited broad genus that is being used for inducing weight loss in humans is pramlintide.

With regard to Appellants' arguments on the reasons for doubting the objective truth of the specification and Appellants' comments on the limitation 'an amount effective to treat obesity' particularly in connection with amylin, a nonpramlintide amylin agonist, a non-pramlintide amylin agonist analogue, a salt of amylin, and a salt of amylin agonist, the following should be noted. The post-filing references of Aronne *et al.* and Smith *et al.* cited by Appellants do not show that administration of any amylin or any non-pramlintide amylin agonist analogue as claimed in the instant claims results in inhibition of weight gain or induction of weight loss in diabetic or non-diabetic human subjects in need of treatment of obesity. As set forth above, at the time of the invention, amylin at a dose varying from about 0.1 to 10 mg was administered to treat patients suffering from anorexia or patients deficient in adipose tissue. See claims and page 13 of Rink *et al.* (WO 9220367). Note that the instantly recited 30 to 300 micrograms per dose of amylin falls within Rink's anorexia-treating dose. The scope of Rink's disclosure includes mammals and therefore does not exclude humans. Appellants themselves have established the direct relevance of Rink's ('106) disclosure to humans via their following statements. Appellants have previously gone on the record with the following (see pages 9, 13 and 14 of Appellants' Appeal Brief filed July 2000) [Emphasis in original]:

.... THE RINK PATENT PROVIDES THAT AMYLIN AND AMYLIN AGONISTS ADMINISTERED AS DESCRIBED AND CLAIMED IN THE PRESENT APPLICATION HAVE "NO MEASURABLE EFFECT" ON FOOD INTAKE.

.... the Rink patent reports that a 1.0 µg/kg dose (**equivalent to about 70µg/dose in an adult human**) had no effect on food intake. [Emphasis in bold added]

Therefore, there was no predictability that administration of a dose varying from about 0.1 to 10 mg of amylin to a human patient would have resulted in inhibition of weight gain or induction of weight loss. Instead of weight loss, one of skill in the art would have expected induction of weight gain. This is yet another reason for doubting the objective truth of the specification. Furthermore, with the art-reported instability of amylin in solution and its tendency to aggregate, one of skill in the art would not have been able to determine an amount effective to reduce weight loss, inhibit weight gain, or relieve obesity without undue experimentation. In view of this, Appellants' description of exemplary amylin agonist compounds alone is insufficient to enable the full scope of the claimed invention. Because of the admitted therapeutic efficacy of amylin against anorexia, one of skill in the art could not have predictably selected non-pramlintide amylin agonist species or non-pramlintide amylin agonist analogue species for treating obesity without considerable amount of undue

experimentation. Thus, in view of level of skill, the state of the art at the time of the invention, and the information in the specification, one of skill would *not* expect that the recited genus could be used in that manner without undue experimentation.

In sum, contrary to Appellants' allegation, a *prima facie* case of lack of scope of enablement has been established by providing sufficient references and specific technical reasons along with the documentation of Appellants' own previous statements. Given the knowledge in the art of the therapeutic effect of amylin against anorexia despite its amylin agonistic characteristics as measured by receptor binding assays and the soleus muscle assay etc., the breadth of the claims, the lack of predictability when viewed in combination with Rink's ('367) showing that the administration of about 0.1 to 10 mg amylin is therapeutic against anorexia, Appellants' own previous acknowledgment that administration of amylin would have lead to *weight gain* rather than *weight decrease* as was known at the time of the invention, Appellants' own previous acknowledgment that amylin and amylin agonists have no measurable effect on food intake, the lack of working examples enabling the full scope of the claimed invention, a considerable amount of non-routine undue experimentation would have been required to reproducibly practice the full scope of the invention, as claimed. Instant claims do not meet the scope of enablement provisions of 35 U.S.C. § 112, first paragraph.

For the reasons delineated above, the art rejection should be sustained.

(II) In response to the rejection of claims 1, 7, 14 and 16 made in paragraph 28 of the Office Action mailed 02/11/08 and maintained in paragraph 13 of the Office Action mailed 04/30/08 under 35 U.S.C § 112, first paragraph, as containing new matter, Appellants submit the following arguments. The Office's rebuttal is provided therein below.

(a) With regard to the Office's lack of descriptive support for the transitional term of art 'consisting' in claim 1, Appellants argue that the term 'consisting' used in claim 1 is a term of art that need not be specifically recited in the specification.

However, it should be noted that it is not merely the limitation 'consisting' in claim 1 that is pertinent to the instant rejection. The new matter rejection pertains to something more than the use of the term 'consisting' in claim 1. Claim 1, as amended, includes the phrase: 'method of treating obesity in a human subject *consisting of administering* to said subject *an amount effective to inhibit weight*

gain or induce weight loss in said human subject of a *composition comprising* an amylin or an amylin agonist ... and a pharmaceutically acceptable carrier' [Emphasis added]. Claim 1 includes the limitation: 'method of treating obesity consisting of administering an amount effective to inhibit weight gain or induce weight loss of composition comprising an amylin or an amylin agonist and a pharmaceutically acceptable carrier'. A method of treatment of obesity 'consisting of' such an administration step *excludes*, for example, simultaneous insulin administration, or insulin administration minutes or hours before or after the administration. However, neither the original six claims, nor the description of the methods of treatment of the instant invention support such a method of treating obesity 'consisting of' administering an effective composition comprising an amylin or an amylin agonist and a pharmaceutically acceptable carrier. For example, the originally filed specification at lines 6-8 of page 9 of the specification states [Emphasis added]:

The present invention is directed to novel methods for treating or preventing obesity in humans *comprising* the administration of an amylin or an amylin agonist, the amylin agonist analogue^{25,28,29} Pro-human amylin.

Pages 30-31 and Table I describe a statistically significant reduction in the mean baseline weight seen after the subcutaneous administration of 60 micrograms TID or 60 micrograms QID of one specific amylin agonist analogue species, pramlintide, to type II diabetic subjects for four weeks, wherein said pramlintide administration was accompanied *with the continued administration of insulin*. The method of treatment of obesity as described in the originally filed specification comprised insulin treatment *and* the administration of a specific dose of pramlintide to type II diabetic patients. This however does not provide descriptive support for the now claimed method of treating obesity in a human in need of treatment for obesity, said method 'consisting' of administering to said subject an amount of a composition as recited comprising an amylin or any amylin agonist and a pharmaceutically acceptable carrier, wherein said amount of the composition is effective to inhibit weight gain or induce weight loss in said subject. It is noted that Appellants have advanced no substantive arguments other than stating that the term 'consisting' in claim 1 is a term of the art that need not be specifically recited in the specification.

(b) Appellants contend that the support for the 'concept' of inhibiting weight gain or inducing weight loss may be found in the specification at lines 9-16 on page 9 of the specification, which discloses the following (Emphasis added by Appellants):

In one aspect, the invention is directed to a method of treating obesity in a human subject comprising administering to said subject an effective amount of an amylin or such an amylin agonist. By "treating or preventing" is meant the management and care of a patient for the purpose of combating the disease, condition or disorder, and includes the administration of an amylin or an amylin agonist to prevent the onset of symptoms or complications, alleviating the symptoms or complications, or eliminating the disease condition or disorder. Treating or preventing obesity therefor includes the inhibition of weight gain and inducing weight loss in patients in need thereof.

Appellants state that further support for the amount of amylin or amylin agonist contemplated in the claims may be found, e.g., at specification page 22, last two lines: "[t]herapeutically effective amounts of an amylin or amylin agonist, such as an amylin agonist analogue, for use in the control of obesity are those that decrease body weight." The amount effective to treat obesity of a composition comprising the required amylin or amylin agonist of the invention is determined by routine methods of pharmaceutical research, and that effectiveness is due to the amylin or amylin agonist in the composition administered to the human subject in need of treatment for obesity.

However, these parts of the specification do not and cannot provide descriptive support for: (a) the claimed 'method of treating obesity in a human subject *consisting of administering* to said subject *an amount effective to inhibit weight gain* or induce weight loss in said human subject of a *composition comprising* an amylin or an amylin agonist ...' in claim 1; (b) for the limitations 'an *amount effective to inhibit weight gain ... of a composition comprising* an obesity relief agent' in claim 7; and (c) the limitations '*salts thereof administered in an amount effective to treat obesity by inhibiting weight gain*' in claim 14 [Emphasis added]. A therapeutically effective amount of an amylin or amylin agonist such as amylin agonist analogue that decreases body weight is not the same in scope as 'an amount of a *composition comprising* an amylin or an amylin agonist effective to *inhibit weight gain* or *induce weight loss*', because the composition recited in claim 1 is allowed to 'comprise' therein other anti-obesity agents other than an amylin or amylin agonist such as exendin, a lipase inhibitor, peptide YY etc. The language 'composition comprising' represents open-ended claim language and therefore, does not exclude additional, unrecited elements. See MPEP 2111.03 [R-1]. See *Moleculon Research Corp. v. CBS, Inc.*, 793 F.2d 1261, 229 USPQ 805 (Fed. Cir. 1986); *In re Baxter*, 656 F.2d 679, 686, 210 USPQ 795, 803 (CCPA 1981); *Ex parte Davis*, 80 USPQ 448, 450 (Bd. App. 1948) ('comprising' leaves 'the claim open for the inclusion of unspecified ingredients *even in major amounts*') [Emphasis added]. Therefore, the limitation 'composition comprising' in claim 1 allows the inclusion of additional anti-obesity agents to be present in the recited composition.

Therefore, an amount of a composition 'comprising' amylin or amylin agonist would include an amount of other anti-obesity agents such as exendin, CCK, peptide YY, or other elements such as insulin, glucagon etc. comprised within the composition. Contrary to Appellants' assertion, the effectiveness of the recited composition cannot be due to amylin or amylin agonist *alone* comprised in the composition.

(c) With regard to the lack of support in claim 14 for 'salts' of amylin or amylin agonist administered in an amount effective to treat obesity by inhibiting weight gain or inducing weight loss in a human subject in need of treatment of obesity, wherein the salt compound is not administered in conjunction with another obesity relief agent, Appellants assert that support for the 'concept of salts' of the compounds of the invention in a *broad sense* may be found at lines 20 and 21 of the specification. Lines 20-21 from page 21 of the instant specification are reproduced below:

the compounds referenced above may form salts with various inorganic and organic acids and bases. Such salts include salts prepared with organic and inorganic acids, for example,

However, what is claimed in claim 14 is not a salt of amylin or amylin agonist, but a method of administering a salt compound of an amylin or amylin agonist in an amount effective to treat obesity by inhibiting weight gain or inducing weight loss in a human subject in need of treatment of obesity, wherein the salt compound is not administered in conjunction with another obesity relief agent. There is lack of support for such a method.

(d) Appellants acknowledge that the dependent claims 2-6, 9-13, 15 and 17 depend from the independent claims 1, 7, 14 and 16, but argue that the Office has provided no express rejection of these dependent claims and therefore the rejection is moot.

As acknowledged by Appellants, claims 2-6, 9-13, 15 and 17 are dependent claims depending from the rejected claims 1, 7, 14 and 16. Since dependent claims are construed to contain *all the limitations* of the claim upon which they depend, it is appropriate to include the dependent claims in the rejection statement.

For the reasons delineated above, the art rejection should be sustained.

(III) In response to the rejection of claims 1-7, 9-14, 16 and 17 made in paragraph 33 of the Office Action mailed 02/11/08 and maintained in paragraph 15 of the Office Action mailed 04/30/08 under 35 U.S.C § 102(a) as being anticipated by Kolterman *et al.* ('220) as evidenced by Tsanev, Appellants submit the following arguments.

(a) Appellants cite case law and MPEP §2131 and assert that in order to anticipate a claim, a single prior art reference must provide each and every element set forth in the claim, and that the identical invention must be shown in complete detail as it is contained in the claim.

(b) Kolterman '220 merely describes the use of an amylin agonist (i.e., pramlintide) for treating type II diabetes mellitus. Kolterman '220 merely demonstrates that administration of an amylin agonist significantly reduces postprandial plasma glucose concentrations in patients with type II diabetes mellitus. Kolterman '220 does not teach the use of an amylin or an amylin agonist for treating obesity or demonstrate a reduction in body weight in those patients administered an amylin or an amylin agonist. Kolterman '220 is silent with regard to the effect of an amylin or an amylin agonist on body weight.

(c) Kolterman '220 at page 7, first paragraph, discloses that the hyperglycemia associated with Type II diabetes can sometimes be reserved or ameliorated by diet or weight loss. With respect to the use of amylin or amylin agonists for treatment of obesity in a subject in need thereof, Kolterman '220 is silent. Whether or not Kolterman '220 discloses that weight loss is beneficial is irrelevant, at least because the Office has failed to state a nexus between administration of an amylin or agonist thereof and treatment for obesity.

(d) In an attempt to cure the deficiency in Kolterman '220, the Office relies on Tsanev to allegedly provide evidence that 80-90% of diabetic patients are obese. However, the 80-90% of obese diabetic patients alleged by Tsanev falls short of the 100% (i.e., always, under any circumstances) criterion required by the claims and required by the law. Thus, Kolterman '220 as evidenced by Tsanev does not provide each and every element of the claimed invention, at least because Kolterman '220 (with or without Tsanev) is silent with respect to treatment of obesity with amylin or agonists thereof, or the intended population for treatment (i.e., human subject in need of treatment for obesity) of the current claims.

Appellants' arguments have been carefully considered, but are not persuasive. Clearly, the Office has set forth a *prima facie* case of anticipation.

Contrary to Appellants' assertion, the prior art method necessarily includes *all* of the elements of the instant claims. As set forth previously, Kolterman *et al.* ('220) taught a method of administering to an insulin-taking type II diabetic human subject a dose of 10, 30, 50, 60 or 150 micrograms per day (i.e., the amount falling in the range recited in the instant claims) of the amylin agonist composition,

pramlintide or ^{25, 28, 29}pro-h-amylin, also known as AC137 (i.e., SEQ ID NO: 1), i.e., the same amylin agonist administered in the instantly claimed method. The composition consists of pramlintide and a pharmaceutically acceptable carrier, and is administered in single or multiple doses, for example, of about 30 micrograms QID, or about 60 micrograms TID or QID, i.e., an amount effective to inhibit weight gain or induce weight loss. See pages 9-11; paragraph bridging pages 20 and 21; page 21; first paragraph on page 19; lines 8-10 on page 19; and the first row reciting 'Insulin-Treated Patients' in each Table of Kolterman *et al.* ('220). Pramlintide is administered subcutaneously 1-4 times a day, before meals. See pages 9 and 22. Kolterman *et al.* ('220) additionally taught that the presence of obesity is a characteristic of 'most patients with Type II diabetes mellitus' (i.e., in need of treatment of obesity). See page 10. Since the structural limitations of the instantly claimed method and *all* of the criteria required by the instant claims are met by the teachings of Kolterman *et al.* ('220), Kolterman's ('220) method is expected to serve necessarily as the instantly claimed method and is expected to bring about the obesity-treating effect, weight gain inhibiting effect, or weight loss-inducing effect.

The Office's position that Kolterman's ('220) method is the same as the Appellants' claimed method is based upon the fact that the method step, the pramlintide compound administered, the amount of the compound administered, the route by which the compound is administered, and the intrinsically obese type II diabetic human patient species to which the pramlintide compound is administered, are the *same* in the two methods. The art-recognized intrinsic obesity being prevalent in 80 to 90% of diabetic patients as disclosed by Tsanev (see abstract), Kolterman's ('220) method of administration of the above-identified therapeutically effective amount (i.e., about 30 micrograms QID, or about 60 micrograms TID or QID, or a dose of 10, 30, 50, 60 or 150 micrograms per day) of the amylin agonist ^{25,28,29}Pro-human amylin to intrinsically obese type 2 diabetic human subject species anticipates the instant claims. That 10-20% of Kolterman's ('220) diabetic patients, also to whom pramlintide is administered, are not expected to be obese is not relevant since an anticipatory reference does not have to teach every species or every embodiment encompassed by the scope of the claims. Given that the method step of the Kolterman's ('220) method and the instant claims are the same, Kolterman's ('220) method is expected to bring about weight gain-inhibiting or weight loss-causing therapeutic effect in the intrinsically obese pramlintide-treated type II diabetic patient. Contrary to Appellants' assertion, the prior art method necessarily includes *all* of the elements of the instant claims. That the determination of inherency in the instant case is certainly not established by

probabilities or possibilities is further evidenced by the teachings of Thompson *et al.* (May 1997). Thompson *et al.* (May, 1997) showed that a method of subcutaneous administration of pramlintide, i.e., ^{25, 28, 29}pro-h-amylin, an analog of human amylin, i.e., an amylin agonist, to patients with type II diabetes requiring insulin, at a dose 60 micrograms QID (i.e., four times a day) or TID (i.e., three times a day) not only improved glycemic control in these patients, but ***also decreased body weight*** concurrently (see abstract). Therefore, Kolterman's ('220) method necessarily served as a method of treating obesity. Since the prior art clearly teaches the instantly claimed method, any assertions of specific functional properties attributed to the amylin agonist pramlintide administered in the claimed method are merely inherent and do not necessarily make the claimed method patentable. *Ex parte Novitski*, 26 USPQ2d 1389 (Bd. Pat. App. & Inter. 1993) (The Board rejected a claim directed to a method for protecting a plant from plant pathogenic nematodes by inoculating the plant with a nematode inhibiting strain of *P. cepacia*. A U.S. patent to Dart disclosed inoculation using *P. cepacia* type Wisconsin 526 bacteria for protecting the plant from fungal disease. Dart was silent as to nematode inhibition but the Board concluded that nematode inhibition was an inherent property of the bacteria. The Board noted that applicant had stated in the specification that Wisconsin 526 possesses an 18% nematode inhibition rating.). In the instant application, the obesity-relief or weight loss-induction is an inherent property inseparable from the administered pramlintide. The two structurally identical pramlintide compounds administered in the two methods (i.e., the prior art method and the instant method) cannot have mutually exclusive properties. The same two methods cannot have mutually exclusive results.

To serve as an anticipation when the reference is silent about the asserted inherent characteristic, such gap in the reference may be filled with recourse to extrinsic evidence. Such evidence must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill.' *Continental Can Co. USA v. Monsanto Co.*, 948 F.2d 1264, 1268, 20 USPQ2d 1746, 1749 (Fed. Cir. 1991). Note that as long as there is evidence of record establishing inherency, failure of those skilled in the art to contemporaneously recognize an inherent property, function or ingredient of a prior art reference does not preclude a finding of anticipation. *Atlas Powder Co. v. IRECO Inc.*, 190 F.3d 1342, 1349, 51 USPQ2d 1943, 1948 (Fed. Cir. 1999). See MPEP 2124. The alleged failure of Kolterman ('220) to expressly mention treatment of obesity as a goal is irrelevant. To the extent the method embodiment in the claimed invention achieves

treatment of obesity, so does the method of Kolterman's ('220). Where the result is a necessary consequence of what was deliberately intended, it is of no import that the article's authors did not appreciate the results. See *Mehl/Biophile International Corp. v. Milgraum*, U.S. Court of Appeals Federal Court, 52 USPQ2d 1303 and 1306, 192 F3d 1362, 1999 citing *W.L. Gore & Assocs. v. Garlack, Inc.*, 721 F.2d 1540, 1548, 220 USPQ 303, 309 (Fed. Cir. 1983).

It is a commonly known fact in the art that type II diabetic patients (80-90% of whom are known to be obese) are 'in need of' obesity. Appellants themselves characterize Type 2 diabetic subjects taking insulin as a particularly difficult to treat obese subject population. See top of page 14 of Appellants' after-final amendment. The English abstract of Tsanev cited on the PTO-892 mailed 06/01/2006, the only disclosure of Tsanev consistently relied upon by the Office throughout the prosecution as evidence of inherency, clearly documented the association between 'diabetes, second type' (i.e., type II or 2 diabetes) and 'obesity' and stated that the two are interrelated. As acknowledged by Appellants throughout the prosecution, including via the Appeal Brief filed 08/07/08 and the reply brief filed 12/11/08, 80-90% of these diabetic patients are obese. This teaching in the Tsanev abstract cited on the PTO-892 mailed 06/01/2006 is consistent with the prior common knowledge in the art. The art at the time of the invention clearly documented that the type of diabetes wherein 80 to 90% are 'obese' is type II diabetes. See the first full paragraph on page 414 of the textbook chapter by Olefsky JM. In: *Harrison's Principles of Internal Medicine*, (Ed) Wilson *et al.*, McGraw-Hill Book Company, 12th Edition, pages 411-416, 1961 (see attachment). It should be noted that the Olefsky textbook chapter is cited herein solely to document the prior common knowledge in the art as explained *supra*, and therefore, it does not constitute a new ground of rejection. Note that where a newly cited reference is added merely as evidence of the prior well known statement made by the examiner, the citation of the reference in the examiner's answer would not constitute a new ground of rejection within the meaning of 37 CFR 41.39(a)(2). See MPEP Section 2144.03.

With regard to the Appellants' statement that Tsanev's disclosure that 80-90% of diabetic patients are obese falls short of the 100% (i.e., always, under any circumstances), the following must be noted. 'A generic claim cannot be allowed to an applicant if the prior art discloses a species falling within the claimed genus'. The species in that case will anticipate the genus. *In re Slayter*, 276 F.2d 408, 411, 125 USPQ 345, 347 (CCPA 1960); *In re Gosteli*, 872 F.2d 1008, 10 USPQ2d 1614 (Fed. Cir. 1989). A genus does not always anticipate a claim to a species within the genus. However, when

the species is clearly named, the species claim is anticipated no matter how many other species are additionally named. In *In re Sivaramakrishnan*, 673 F.2d 1383, 213 USPQ 441 (CCPA 1982), the claims were directed to polycarbonate containing cadmium laurate as an additive. The court upheld the Board's finding that a reference specifically naming cadmium laurate as an additive amongst a list of many suitable salts in polycarbonate resin anticipated the claims. The applicant had argued that cadmium laurate was only disclosed as representative of the salts and was expected to have the same properties as the other salts listed while, as shown in the application, *cadmium laurate had unexpected properties*. The court held that it *did not matter that the salt was not disclosed as being preferred, the reference still anticipated the claims* and because the claim was anticipated, *the unexpected properties were immaterial*. Although the instant claims are method claims, in the instant application, the prior art disclosure of a method comprising or consisting of the administration of 30 or micrograms of the amylin agonist,^{25,28,29} Pro-human amylin, to 80-90% of the human diabetic patients anticipates the instantly claimed method. The claims are anticipated because the administered^{25,28,29} Pro-human amylin also inherently exerted obesity-relieving properties in said method. See also *Ex parte Novitski*, 26 USPQ2d 1389 (Bd. Pat. App. & Inter. 1993) (The Board rejected a claim directed to a method for protecting a plant from plant pathogenic nematodes by inoculating the plant with a nematode inhibiting strain of *P. cepacia*. A U.S. patent to Dart disclosed inoculation using *P. cepacia* type Wisconsin 526 bacteria for protecting the plant from fungal disease. Dart was silent as to nematode inhibition but the Board concluded that nematode inhibition was an inherent property of the bacteria. The Board noted that applicant had stated in the specification that Wisconsin 526 possesses an 18% nematode inhibition rating.). In the instant application, the obesity-relief or weight loss-induction is an intrinsic property inseparable from the administered pramlintide. The two structurally identical pramlintide compounds administered in the two methods (i.e., the prior art method and the instant method) cannot have mutually exclusive properties. As set forth above, this is evidenced by the teachings of Thompson *et al.* (May 1997).

In the instant application, it is important to note that the *human patients used in the instant specification for treatment of obesity via administration of pramlintide are indeed type II diabetic human patients*. Thus, the prior art disclosure is commensurate in scope with the instant disclosure with regard to the type 2 diabetic human subject population used, the pramlintide compound administered, the amount and the frequency of pramlintide administered, to the type 2 diabetic human patients.

In the instant case, the claims are drawn to a method of treatment of obesity that uses generic human subjects. The method is not limited to treating obesity in non-diabetic obese human patients, but encompasses treating obesity in type II diabetic human patients, 80-90% of whom are known in the art to have intrinsic obesity. In other words, treatment of obesity in type II diabetic human patients is just one of the species or embodiments encompassed within the scope of the genus of human subjects in need of such treatment. That 10-20% of the prior art diabetic patients, to whom pramlintide is administered, are not expected to be obese is not relevant since an anticipatory reference has to teach only one species or one embodiment encompassed by the scope of the genus claims. Under the principles of inherency, a reference may be directed to an entirely different problem than the one addressed by the inventor, or may be from an entirely different field of endeavor than that of the claimed invention, yet the reference is still anticipatory if it explicitly or inherently discloses every limitation recited in the claims. See *State Contracting & Eng'g Corp. v. Condotta America, Inc.*, 346 F.3d 1057, 1068, 68 USPQ2d 1481, 1488 (Fed. Cir. 2003). Appellants appear to be arguing that in order to be anticipatory, a prior art reference has to teach each and every species or embodiment encompassed within the scope of the claims. The argument is not persuasive.

For the reasons delineated above, the art rejection should be sustained.

(IV) In response to the rejection of claims 7, 14, 16 and 17 made in paragraph 35 of the Office Action mailed 02/11/08 and maintained in paragraph 17 of the Office Action mailed 04/30/08 under 35 U.S.C § 102(b) over Kolterman *et al.* (*Diabetologia* 39: 492-499, April, 1996) (Kolterman *et al.*, 1996) as evidenced by Itasaka *et al.* (*Psychiatr. Clin. Neurosci.* 54: 340-341, June 2000), Appellants submit the following arguments.

(a) Kolterman 1996 merely describes the use of an amylin agonist, pramlintide, for treating patients with insulin-dependent diabetes mellitus and demonstrates *inter alia* that administration of the amylin agonist significantly reduces postprandial plasma glucose concentrations. Kolterman 1996 discloses neither the use of the amylin agonist for treating obesity nor a reduction in body weight in those patients administered the amylin agonist. Kolterman 1996 does not report the weight of the subjects at the end of the study and nothing in the reference indicates that pramlintide had any effect on the weight of the subjects. Kolterman 1996 is silent with regard to the effect of the amylin agonist on body weight. In an effort to cure the deficiencies of Kolterman 1996, the Examiner relies

on Itasaka to allegedly provide a correlation between body mass index (BMI) and obesity. However, nothing in Kolterman 1996 (with or without evidence of Itasaka) suggests that an amylin agonist can be useful in the treatment of obesity, or in the selection of a subject population for such method of treatment. The patient population of Kolterman 1996 is not necessarily the same as the claimed subject, *i.e.*, a subject in need of treatment for obesity.

(b) The fact that a certain result or characteristic may occur or be present in the prior art is not sufficient to establish the inherency of that result or characteristic. *In re Rijckaert*, 9 F.3d 1531, 1534 (Fed. Cir. 1993). "To establish inherency, the extrinsic evidence must make clear that the missing descriptive matter is necessarily present in the thing described in the references, and that it would be so recognized by persons of ordinary skill. Inherency, however, may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient." *In re Robertson* 169 F.3d 743,745 (Fed. Cir. 1999).

Appellants' arguments have been carefully considered, but are not persuasive. Clearly, the Office has set forth a *prima facie* case of anticipation.

Contrary to Appellants' assertion, the prior art method necessarily includes *all* of the elements of the instant claims. As set forth previously, Kolterman *et al.* (1996) taught a method of subcutaneous administration of 30, 100, or 300 µg of pramlintide composition or AC137 (*i.e.*,^{25, 28, 29}pro-h-amylin), a human amylin analogue, to human patients with insulin-dependent diabetes mellitus or IDDM who are on insulin. Pramlintide is administered three times daily for a period of 14 days. See abstract; and page 493. The mean body weight \pm SEM of diabetic patients included in Kolterman's (1996) method who were administered subcutaneously with 30 micrograms, 100 micrograms, and 300 micrograms of pramlintide, three times a day for 14 days, was 70.6 ± 2.7 , 74.4 ± 2.5 , and 75.7 ± 2.6 respectively, a body weight similar to the 70 kg body weight of the human patient disclosed at lines 4-8 of page 23 of the substitute instant specification; and paragraph bridging pages 23 and 24 and lines 3-7 on page 24 of Appellants' response filed December 2002. Note that the human patient in need of the recited treatment according to the instant invention is expressly identified in the instant specification as one having a body weight of 79 kg. For example, the recited therapeutic amount range of 'about 0.1 milligrams per day to about 1 milligram per day', or 'about 0.01 to about 5 mg/day', or 0.03 to about 5 mg/day of the amylin agonist or amylin agonist analogue, pramlintide, administered is specifically "for a 70 kg patient". See lines 4-8 of page 23 of the substitute instant

specification; and paragraph bridging pages 23 and 24 and lines 3-7 on page 24 of Appellants' response filed December 2002. Therefore, the 70.6 to 75.7 kg diabetic patients from Kolterman's (1996) study qualify as 'human subjects in need thereof' as recited in the instant claims. Additionally, even body mass index (BMI)-wise, Kolterman's (1996) diabetic subjects meet the limitation 'human subjects in need of treatment of obesity' as recited in the instant claims, because the diabetic subjects included in Kolterman's method (1996) had a BMI of up to 27. See second full paragraph under 'Subjects, materials and methods'. Therefore, Kolterman's (1996) diabetic subjects having a BMI at least in the range of 24 up to 27 do qualify as obese diabetic subjects in light of what is known in the art. For example, Itasaka *et al.* teach that a BMI of 24.0 to 26.4 represents mild obesity and 26.4 and heavier (i.e., including a BMI of 26.4 to 27) represents obesity in humans (see abstract of Itasaka *et al.*). Note that Kolterman's (1996) pramlintide composition did not comprise another obesity relief agent, but consisted of or consisted essentially of pramlintide. The pramlintide composition was injected subcutaneously to the diabetic human patients (see the section 'Study design') and therefore is expected to inherently contain a pharmaceutically acceptable carrier therein. The amount administered was 30 micrograms three times a day to 'about 0.1 milligrams' or 300 micrograms per day. See the section 'Study design'; Table 1; and paragraph therebelow. Clearly, Kolterman's (1996) subcutaneous administration of a therapeutically effective amount of the amylin agonist^{25,28,29}Pro-human amylin to diabetic human subjects weighing 70 kg or more, or having a BMI falling in the BMI range of 24 up to 27 anticipates the instant claims. Thus, the very active step recited in the instantly claimed method was disclosed and practiced by Kolterman *et al.* in April, 1996. The prior art method of administering the above-explained amount of the amylin agonist^{25,28,29}Pro-human amylin (pramlintide or SEQ ID NO: 1) to diabetic human subjects weighing 70 kg or more, and/or having a BMI falling in the range of 24 up to 27 necessarily serves as the Appellants' method. Given that the method step in Kolterman's (1996) method and the instant claims are the *same* and the amount of pramlintide administered are the *same*, Kolterman's (1996) method is expected to necessarily bring about the same therapeutic effect in the pramlintide-treated diabetic patients as defined in the instant invention, i.e., by controlling body weight for cosmetic purposes, or by improving bodily appearance in the diabetic patients, or by inhibiting weight gain. That the determination of inherency in the instant case is certainly not established by probabilities or possibilities is further evidenced by the teachings of Rattner *et al.* (*Exp. Clin. Endocrinol. Diabetes* 113: 199-204, 2005) (Rattner *et al.* 2005). The

reference of Rattner *et al.* (2005) is set forth herein solely to address Appellants' arguments. The reference of Rattner *et al.* (2005), which is co-authored by the inventor OG Kolterman, show that subcutaneous administration of 30 or 60 micrograms of TID or QID pramlintide to insulin-taking IDDM patients having a body weight of 76.0 ± 14.3 kg or a BMI of > 25 kg/m², concurrently induced *a significant decline in weight*. See sections 'Subjects and Methods'; Results; Table 1; and Figure 1B of Rattner *et al.* (2005). Therefore, Kolterman's (1996) method necessarily served as a method of treating obesity. It is particularly noted that Appellants have advanced no arguments with regard to the teachings of Rattner *et al.* (2005), the reference that was cited to show that the missing inherent matter is necessarily present in the method thing described in the prior art reference of Kolterman *et al.* (1996).

In sum, since the prior art clearly teaches the instantly claimed method, any assertions of specific functional properties attributed to the amylin agonist pramlintide administered in the claimed method are merely inherent and do not necessarily make the claimed method patentable. *Ex parte Novitski*, 26 USPQ2d 1389 (Bd. Pat. App. & Inter. 1993) (The Board rejected a claim directed to a method for protecting a plant from plant pathogenic nematodes by inoculating the plant with a nematode inhibiting strain of *P. cepacia*. A U.S. patent to Dart disclosed inoculation using *P. cepacia* type Wisconsin 526 bacteria for protecting the plant from fungal disease. Dart was silent as to nematode inhibition but the Board concluded that nematode inhibition was an inherent property of the bacteria. The Board noted that applicant had stated in the specification that Wisconsin 526 possesses an 18% nematode inhibition rating.). In the instant application, the obesity-relief or weight loss-induction is an inherent property inseparable from the administered pramlintide. Since the structural limitations of the instantly claimed method and *all* of the criteria required by the instant claims are met by the disclosure of Kolterman *et al.* ('1996), Kolterman's ('1996) method is expected to serve necessarily as the instantly claimed method and is expected to bring about the weight gain-inhibiting effect, weight loss-inducing effect, or obesity-treating effect. The two structurally identical pramlintide compounds administered in the two methods (i.e., the prior art method and the instant method) cannot have mutually exclusive properties. The same two methods cannot have mutually exclusive results.

'To serve as an anticipation when the reference is silent about the asserted inherent characteristic, such gap in the reference may be filled with recourse to extrinsic evidence. Such evidence must make clear that the missing descriptive matter is necessarily present in the thing

described in the reference, and that it would be so recognized by persons of ordinary skill.’ *Continental Can Co. USA v. Monsanto Co.*, 948 F.2d 1264, 1268, 20 USPQ2d 1746, 1749 (Fed. Cir. 1991). Note that as long as there is evidence of record establishing inherency, failure of those skilled in the art to contemporaneously recognize an inherent property, function or ingredient of a prior art reference does not preclude a finding of anticipation. *Atlas Powder Co. v. IRECO Inc.*, 190 F.3d 1342, 1349, 51 USPQ2d 1943, 1948 (Fed. Cir. 1999). See MPEP 2124. Itasaka’s extrinsic evidence makes clear that the missing descriptive matter, i.e., a BMI of 24.0 to 26.4 as present in Kolterman’s diabetic patients represents mild obesity and a BMI of 26.4 and heavier as present in Kolterman’s diabetic patients (i.e., including a BMI of 26.4 to 27) represents obesity in humans, and therefore is necessarily present in the method thing described by Kolterman *et al.* (1996). The method of Kolterman *et al.* (1996) clearly anticipates the claimed method of the instant invention, because Kolterman *et al.* (1996) taught the very step of the instantly claimed method in human IDDM patients. The alleged failure of Kolterman *et al.* (1996) to expressly mention treatment of obesity as a goal is irrelevant. To the extent the method embodiment in the claimed invention achieves treatment of obesity, so does the method of Kolterman *et al.* (1996). Where the result is a necessary consequence of what was deliberately intended, it is of no import that the article’s authors did not appreciate the results. See *Mehl/Biophile International Corp. v. Milgraum*, U.S. Court of Appeals Federal Court, 52 USPQ2d 1303 and 1306, 192 F3d 1362, 1999 citing *W.L. Gore & Assocs. v. Garlack, Inc.*, 721 F.2d 1540, 1548, 220 USPQ 303, 309 (Fed. Cir. 1983).

‘A generic claim cannot be allowed to an applicant if the prior art discloses a species falling within the claimed genus’. The species in that case will anticipate the genus. *In re Slayter*, 276 F.2d 408, 411, 125 USPQ 345, 347 (CCPA 1960); *In re Gosteli*, 872 F.2d 1008, 10 USPQ2d 1614 (Fed. Cir. 1989). A genus does not always anticipate a claim to a species within the genus. However, when the species is clearly named, the species claim is anticipated no matter how many other species are additionally named. In *In re Sivaramakrishnan*, 673 F.2d 1383, 213 USPQ 441 (CCPA 1982), the claims were directed to polycarbonate containing cadmium laurate as an additive. The court upheld the Board’s finding that a reference specifically naming cadmium laurate as an additive amongst a list of many suitable salts in polycarbonate resin anticipated the claims. The applicant had argued that cadmium laurate was only disclosed as representative of the salts and was expected to have the same properties as the other salts listed while, as shown in the application, *cadmium laurate had unexpected properties*. The court held

that it *did not matter that the salt was not disclosed as being preferred, the reference still anticipated the claims* and because the claim was anticipated, *the unexpected properties were immaterial*. Although the instant claims are method claims, in the instant application, the prior art disclosure of a method comprising or consisting of the subcutaneous administration of 30 micrograms, 100 micrograms, and 300 micrograms of pramlintide, three times a day for 14 days of the amylin agonist, ^{25,28,29}Pro-human amylin, to the human diabetic patient species weighing 70 kg or more, and/or having a BMI falling in the range of 24 up to 27 anticipates the instantly claimed method which uses generic human subjects in need of treatment of obesity. The claims are anticipated because the administered ^{25,28,29}Pro-human amylin also inherently exerted obesity-relieving properties in said method. See also *Ex parte Novitski*, 26 USPQ2d 1389 (Bd. Pat. App. & Inter. 1993) (The Board rejected a claim directed to a method for protecting a plant from plant pathogenic nematodes by inoculating the plant with a nematode inhibiting strain of *P. cepacia*. A U.S. patent to Dart disclosed inoculation using *P. cepacia* type Wisconsin 526 bacteria for protecting the plant from fungal disease. Dart was silent as to nematode inhibition but the Board concluded that nematode inhibition was an inherent property of the bacteria. The Board noted that applicant had stated in the specification that Wisconsin 526 possesses an 18% nematode inhibition rating.). In the instant application, the obesity-relief or weight loss-induction is an intrinsic property inseparable from the administered pramlintide. The two structurally identical pramlintide compounds administered in the two methods (i.e., the prior art method and the instant method) cannot have mutually exclusive properties. As set forth above, this is evidenced by the teachings of Rattner *et al.* (2005), which is co-authored by the inventor OG Kolterman.

In the instant case, the claims are drawn to a method that uses generic human subjects in need of treatment of obesity. The generic limitation 'human subject' in the instant claims does not exclude 'a 70 kg patient'. The method is not limited to treating obesity in non-diabetic obese human patients, but encompasses treating obesity in type I diabetic human patients weighing 70 kg or more, and/or having a BMI falling in the range of 24 up to 27. In other words, treatment of obesity in type I diabetic human patients is just one of the species or embodiments encompassed within the scope of the genus of human subjects in need of such treatment. An anticipatory reference has to teach only one species or one embodiment encompassed by the scope of the genus claims. Furthermore, under the principles of inherency, a reference may be directed to an entirely different problem than the one addressed by the inventor, or may be from an entirely different field of endeavor than that of the claimed invention, yet

the reference is still anticipatory if it explicitly or inherently discloses every limitation recited in the claims. See *State Contracting & Eng'g Corp. v. Condotte America, Inc.*, 346 F.3d 1057, 1068, 68 USPQ2d 1481, 1488 (Fed. Cir. 2003). Appellants appear to be arguing that in order to be anticipatory, a prior art reference has to teach each and every species or embodiment encompassed within the scope of the claims. The argument is not persuasive.

For the reasons delineated above, the art rejection should be sustained.

(V) In response to the rejection of claims 7, 14, 16 and 17 made in paragraph 26 of the Office Action mailed 02/11/08 and maintained in paragraph 11 of the Office Action mailed 04/30/08 under the judicially created doctrine of obviousness-type double patenting over claims 34 and 35 of Gaeta *et al.* ('411) as evidenced by Tsanev, Appellants submit the following arguments.

(a) The alleged prior art does not include all of the elements of the instant claims as required by the law. The references provide no guidance concerning the identification of or intent to treat a subject in need of treatment for obesity. The predecessor court to the Federal Circuit held that the inherency of an advantage and its obviousness are entirely different questions, that which may be inherent is not necessarily known, and that obviousness cannot be predicated on what is unknown.

(b) Claims 7, 14, 16 and 17 are directed to methods for treating obesity in a human subject in need of such treatment, which methods require administration of a composition or compound containing an amylin or an amylin agonist, wherein the amount of the composition or compound administered is effective to treat obesity by inhibiting weight gain or inducing weight loss, and wherein the subject is in need of treatment for obesity. Claims 34 and 35 of Gaeta are merely directed to methods for the treatment of diabetes mellitus in a mammal comprising the administration of a therapeutically effective amount of a particular amylin agonist analogue. Gaeta is silent with respect to the treatment of obesity.

(c) In an attempt to cure the deficiency of claims 34 and 35 of Gaeta, the Office relies on Tsanev to assert that 80-90% of diabetic patients are obese. Even in view of Tsanev, a claim to treating diabetes mellitus with an amylin agonist analogue (i.e., claims of Gaeta) does not teach or suggest treating subjects as currently claimed. Nothing in the cited claims teaches or

suggests the identification of or intent to treat a subject in need of treatment for obesity. The courts have held that the phrase 'in need thereof' as recited in independent claims 7, 14 and 16 is meaningful, and that 'the claims' recitation of a patient or a human 'in need' gives life and meaning to the preambles' statement of purpose." *Jansen v. RexallSundown, Inc.* 342 F.3d 1329, 1333 (Fed. Cir. 2003). Since the cited claims do not teach or suggest treating obesity, the intent to treat human subjects in need of treatment for obesity, or the use of an amount effective to treat obesity, a skilled artisan would have no expectation of success for the claimed invention in view of the cited claims. In this regard, "[r]ejections on obviousness grounds cannot be sustained by mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness." *KSR*, 127 S.Ct. at 1741 (quoting *In re Kahn* 441 F.3d 977, 988 (Fed. Cir. 2006)). The prior art must still suggest a predictable outcome to establish a *prima facie* case of obviousness. See, e.g., *Takeda Chemical Industries, LM v. Alphapharm Pty., Ltd.* 492 F.3d 1350, 83 U.S.P.Q.2d 1169 (Fed. Cir. 2007).

(d) The disclosure of Gaeta, whether evidenced by Tsanev or not, is silent with respect to the treatment of obesity. Gaeta did not disclose that an amylin or amylin agonist is useful for treating obesity in a human in need of treatment thereof. The Office's reliance on inherency in the context of anticipation in the rejection(s) is contrary to the law. Anticipation based on inherency is appropriate only when the prior art relied upon necessarily includes all of the elements of the claims in question and is the natural result of following the instructions or examples of the prior art. See, *Atofina v. GreatLakes Chemical Corp.*, 441 F.3d 991, 78 USPQ2d 1417, 1424 (Fed. Cir. 2006); *SmithKline Beecham Corp. v. Apotex Corp.*, 403 F.3d 1331, 1334, 74 USPQ2d 1398, 1407 (Fed. Cir. 2005) (citing *Schering Corp. v. Geneva Pharms., Inc.*, 339 F.3d 1373, 1377, 67 USPQ2d 1664, 1667 (Fed. Cir. 2003)). The Court in *Schering* relied in part on the decision *In re Cruciferous Sprouts Litigation*, 301 F.3d 1343, 1351, 64 USPQ2d 1202, 1206 (Fed. Cir. 2002) wherein it was noted that to demonstrate inherency, it was necessary to show that the prior art necessarily, always functions in accordance with the claims addressed. The requirement that the teaching of a reference always, under any circumstances, necessarily satisfies the recitation of the claims to make out a case of inherent anticipation was reaffirmed by the Federal Circuit in *Abbott Laboratories v. Baxter Pharmaceutical Products, Inc.*, 471 F.3d 1363, 1368 (Fed. Cir. 2006). It is well settled that a determination of inherency cannot be

established by probabilities or possibilities, but that it is incumbent upon the Examiner to establish the inevitability of the inherency which is propounded. *In re Oelrich*, 666 F.2d 578, 581,212 USPQ 323,326 (CCPA 1981); *In re Wilding*, 535 F.2d 631, 635-36, 190 USPQ 59, 63-64 (CCPA 1976). Tsanev discloses that 80-90% of diabetic patients are obese, which falls short of the 100% (i.e., always, under any circumstances) criterion required by the present claims and required by the law. Accordingly, claims 34 and 35 of Gaeta support neither *prima facie* obviousness nor anticipation with regard to the claimed invention.

(e) The Office improperly asserts that the prior method necessarily includes all of the elements of the instant claims as evidenced by Thompson *et al.* (*Diabetes* 46: Suppl. 1, page 30A, 0116, 02 May 1997) (Thompson 1997). Appellants had filed a declaration under 37 C.F.R. § 1.131 in the response to Office Action filed December 2, 2002, which demonstrates that the current application antedates Thompson 1997 and was inventors' own work. Accordingly, Thompson 1997 is unavailable as prior art against the current application. More particularly, Thompson 1997 cannot be used as evidence of an alleged inherency because the present invention antedates Thompson 1997. See *In re Shetty (Id.)*. Thus, the Office has failed to provide evidence or argument with any rational underpinning that the current claims are obvious in view of Gaeta as evidenced by Tsanev. Whatever else is taught by Gaeta and Tsanev, the references do not teach or suggest a method of treating obesity in a subject in need of treatment thereof.

The Office submits the following rebuttal to Appellants' arguments:

Contrary to Applicants' assertion, the prior art method necessarily includes *all* of the elements of the instant claims. As set forth previously, the '411 patent's patients seen by a medical practitioner, i.e., humans having diabetes mellitus, was administered with a therapeutically effective amount of the amylin agonist of claim 19, ^{25,28,29}Pro-human amylin (SEQ ID NO: 1 or pramlintide), the same amylin agonist analogue recited in instant claim 17. The method of treatment claimed in claims 34 and 35 of the '411 patent includes administering to such a patient with diabetes mellitus a therapeutically effective amount of the amylin agonist of claim 19 of the '411 patent, ^{25,28,29}Pro-human amylin (SEQ ID NO: 1 or pramlintide). The portion of the disclosure of the '411 patent at second paragraph under 'Summary of the Invention' supporting the limitations 'diabetes mellitus' and 'administration of an amylin agonist analogue' include insulin-requiring diabetes mellitus and administration of an amylin agonist analogue alone (i.e., consisting of) or in conjunction with (comprising or consisting essentially

of) insulin or a glucagon, i.e., not in conjunction with another obesity relief agent. The portion of the disclosure of the '411 patent at lines 53-59 in column 8 supporting the limitation 'therapeutically effective amount' of the amylin agonist includes the dosage units of 0.1 to 5 mg or 0.5 to 1.0 mg of the amylin agonist. The amount effective to inhibit weight gain or induce weight loss, i.e., treat obesity, encompassed in the instant claims as described in the instant application of about 0.01 milligrams to about 5 milligrams per day, about 0.05 milligrams to about 2 milligrams per day, about 0.1 milligrams to about 1 milligram per day, or 300 micrograms per dose, falls within the range disclosed in the '411 patent. Given the art-known prevalence of intrinsic obesity in as many as 80% to 90% of diabetic patients as disclosed by Tsanev, 80-90% of the human diabetic patients used in the method disclosed in the '411 patent qualified as human patients in need of treatment for obesity. Therefore, the method of the '411 patent comprising or consisting of the administration of 0.1 to 5 mg, or 0.5 to 1.0 mg of the amylin agonist,^{25,28,29} Pro-human amylin alone or in conjunction with insulin or glucagon, to 80-90% of the human diabetic patients anticipates the instant claims. Given that the method step of the '411 patent and the instant claims are the same, the amylin agonist analogue pramlintide used and its amount administered are the same, and the human diabetic patients used are the same (80-90% of whom are known to be obese), the method of the '411 patent is expected to necessarily bring about a weight gain-inhibiting effect, weight loss-inducing effect, or obesity-treating effect in the intrinsically obese diabetic patient administered with a therapeutically effective amount of the pramlintide as claimed in the instant invention. Since the structural limitations of the instantly claimed method and *all* of the criteria required by the instant claims are met by the disclosure of Gaeta *et al.* ('411), Gaeta's ('411) method is expected to serve necessarily as the instantly claimed method and is expected to bring about the weight gain inhibiting effect, weight loss-inducing effect, or obesity-treating effect.

That the determination of inherency in the instant case is not established by probabilities or possibilities is further evidenced by the teachings of Thompson *et al.* (*Diabetes* 46: Suppl. 1, page 30A, 0116, 02 May 1997) (Thompson *et al.* May, 1997). The reference of Thompson *et al.* is cited solely to rebut Appellants' arguments by showing that the missing inherent matter is necessarily present in the method thing described in the prior art reference of '411 patent. Thompson *et al.* (May, 1997) showed that a method of subcutaneous administration of pramlintide, i.e.,^{25, 28, 29} pro-h-amylin, an analog of human amylin, i.e., the same amylin agonist used in the instant invention, to patients with type II diabetes requiring insulin, at a dose 60 micrograms QID (i.e., four times a day) or TID (i.e., three times a day) not

only improved glycemic control in these patients, ***but also decreased body weight*** concurrently (see abstract). Therefore, the method of the '411 patent necessarily served as a method of treating obesity. With regard Appellants' statement that Thompson (1997) cannot be used as evidence of an alleged inherency because the present invention antedates Thompson 1997, it should be noted that the critical date of extrinsic evidence need *not* antedate the filing date of the instant application. See MPEP § 2124.

It is a commonly known fact in the art that type II diabetic patients (80-90% of whom are known to be obese) are 'in need of' obesity. Appellants themselves characterize Type 2 diabetic subjects taking insulin as a particularly difficult to treat obese subject population. See top of page 14 of Appellants' after-final amendment. The English abstract of Tsanev cited on the PTO-892 mailed 06/01/2006, the only disclosure of Tsanev consistently relied upon by the Office throughout the prosecution as evidence of inherency, clearly documented the association between 'diabetes, second type' (i.e., type II or 2 diabetes) and 'obesity' and stated that the two are interrelated. As acknowledged by Appellants throughout the prosecution, including via the Appeal Brief filed 08/07/08 and the reply brief filed 12/11/08, 80-90% of these diabetic patients are obese. This teaching in the Tsanev abstract cited on the PTO-892 mailed 06/01/2006 is consistent with the prior common knowledge in the art. The art at the time of the invention clearly documented that the type of diabetes wherein 80 to 90% are 'obese' is type II diabetes. See the first full paragraph on page 414 of the textbook chapter by Olefsky JM. *In: Harrison's Principles of Internal Medicine*, McGraw-Hill Book Company, (Ed) Wilson *et al.*, 12th Edition, pages 411-416, 1961 (see attachment). It should be noted that the Olefsky textbook chapter is cited herein solely to document the prior common knowledge in the art as explained *supra*, and therefore, it does not constitute a new ground of rejection. Note that where a newly cited reference is added merely as evidence of the prior well known statement made by the examiner, the citation of the reference in the examiner's answer would not constitute a new ground of rejection within the meaning of 37 CFR 41.39(a)(2). See MPEP Section 2144.03.

With regard to the Appellants' statement that Tsanev's disclosure that 80-90% of diabetic patients are obese falls short of the 100% (i.e., always, under any circumstances), the following must be noted. 'A generic claim cannot be allowed to an applicant if the prior art discloses a species falling within the claimed genus'. The species in that case will anticipate the genus. *In re Slayter*, 276 F.2d 408, 411, 125 USPQ 345, 347 (CCPA 1960); *In re Gosteli*, 872 F.2d 1008, 10 USPQ2d 1614 (Fed. Cir. 1989). A genus does not always anticipate a claim to a species within the genus. However, when the species is clearly

named, the species claim is anticipated no matter how many other species are additionally named. In *In re Sivaramakrishnan*, 673 F.2d 1383, 213 USPQ 441 (CCPA 1982), the claims were directed to polycarbonate containing cadmium laurate as an additive. The court upheld the Board's finding that a reference specifically naming cadmium laurate as an additive amongst a list of many suitable salts in polycarbonate resin anticipated the claims. The applicant had argued that cadmium laurate was only disclosed as representative of the salts and was expected to have the same properties as the other salts listed while, as shown in the application, *cadmium laurate had unexpected properties*. The court held that it *did not matter that the salt was not disclosed as being preferred, the reference still anticipated the claims* and because the claim was anticipated, *the unexpected properties were immaterial*. Although the instant claims are method claims, in the instant application, the prior art disclosure of a method comprising or consisting of the administration of 0.1 to 5 mg, or 0.5 to 1.0 mg of the amylin agonist, ^{25,28,29}Pro-human amylin alone or in conjunction with insulin or glucagon, to 80-90% of the human diabetic patients anticipates the instantly claimed method. The claims are anticipated because the administered ^{25,28,29}Pro-human amylin also inherently exerted obesity-relieving properties in said method. See also *Ex parte Novitski*, 26 USPQ2d 1389 (Bd. Pat. App. & Inter. 1993) (The Board rejected a claim directed to a method for protecting a plant from plant pathogenic nematodes by inoculating the plant with a nematode inhibiting strain of *P. cepacia*. A U.S. patent to Dart disclosed inoculation using *P. cepacia* type Wisconsin 526 bacteria for protecting the plant from fungal disease. Dart was silent as to nematode inhibition but the Board concluded that nematode inhibition was an inherent property of the bacteria. The Board noted that applicant had stated in the specification that Wisconsin 526 possesses an 18% nematode inhibition rating.). In the instant application, the obesity-relief or weight loss-induction is an intrinsic property inseparable from the administered pramlintide. The two structurally identical pramlintide compounds administered in the two methods (i.e., the prior art method and the instant method) cannot have mutually exclusive properties. As set forth above, this is evidenced by the teachings of Thompson *et al.* (1997) who showed that a method of subcutaneous administration of pramlintide, i.e., ^{25, 28, 29}pro-h-amylin, an analog of human amylin, i.e., an amylin agonist, to patients with type II diabetes requiring insulin, at a dose 60 micrograms QID or TID not only improved glycaemic control in these patients, but also decreased body weight concurrently (see abstract). Therefore, the prior art method necessarily served as a method of treating obesity. The same two methods (i.e., the prior art method and the instant method) cannot have mutually exclusive results.

In the instant application, it is important to note that the *human patients used in the instant specification for treatment of obesity via administration of pramlintide are indeed type II diabetic human patients*. Thus, the prior art disclosure is commensurate in scope with the instant disclosure with regard to the type 2 diabetic human subject population used, the pramlintide compound administered, the amount and frequency of pramlintide administered, to the type 2 diabetic human patient species.

In the instant case, the claims are drawn to a method that uses generic human subjects. The method is not limited to treating obesity in non-diabetic obese human patients, but encompasses treating obesity in type II diabetic human patients, 80-90% of whom are known in the art to have intrinsic obesity. In other words, treatment of obesity in type II diabetic human patients is just one of the species or embodiments encompassed within the scope of the genus of human subjects in need of such treatment. That 10-20% of prior art diabetic patients, to whom pramlintide is administered, are not expected to be obese is not relevant since an anticipatory reference has to teach only one species or one embodiment encompassed by the scope of the genus claims. Under the principles of inherency, a reference may be directed to an entirely different problem than the one addressed by the inventor, or may be from an entirely different field of endeavor than that of the claimed invention, yet the reference is still anticipatory if it explicitly or inherently discloses every limitation recited in the claims. See *State Contracting & Eng'g Corp. v. Condotte America, Inc.*, 346 F.3d 1057, 1068, 68 USPQ2d 1481, 1488 (Fed. Cir. 2003). Appellants appear to be arguing that in order to be anticipatory, a prior art reference has to teach each and every species or embodiment encompassed within the scope of the instant claims. The argument is not persuasive.

For the reasons delineated above, the rejection should be sustained.

(VI) In response to the rejection of claims 7, 14 and 16 made in paragraph 27 of the Office Action mailed 02/11/08 and maintained in paragraph 12 of the Office Action mailed 04/30/08 under the judicially created doctrine of obviousness-type double patenting over claims 11 and 13 of Beumont *et al.* ('008) as evidenced by Tsanev, Appellants submit the following argument. In view of the similarity of the current rejection to the double patenting rejection over Gaeta discussed above, arguments provided above in relation to that rejection are reiterated. Arguments provided for the double patenting rejection over Gaeta ('411) are hereby reiterated. Appellants are referred to section V above for the Office's response.

(VII) In response to the rejection of claims 7, 14 and 16 made in paragraph 34 of the Office Action mailed 02/11/08 and maintained in paragraph 16 of the Office Action mailed 04/30/08 under 35 U.S.C § 102(e)(2) over Beumont *et al.* ('008) as evidenced by Tsanev, Appellants reiterate the same arguments that they have presented on the obviousness double patenting rejection over US patent 5,321,008. Appellants are referred to sections V and VI above for the Office's response.

'To serve as an anticipation when the reference is silent about the asserted inherent characteristic, such gap in the reference may be filled with recourse to extrinsic evidence. Such evidence must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill.' *Continental Can Co. USA v. Monsanto Co.*, 948 F.2d 1264, 1268, 20 USPQ2d 1746, 1749 (Fed. Cir. 1991). Note that as long as there is evidence of record establishing inherency, failure of those skilled in the art to contemporaneously recognize an inherent property, function or ingredient of a prior art reference does not preclude a finding of anticipation. *Atlas Powder Co. v. IRECO Inc.*, 190 F.3d 1342, 1349, 51 USPQ2d 1943, 1948 (Fed. Cir. 1999). See MPEP 2124. Tsanev's extrinsic evidence makes clear that the missing descriptive matter, i.e., prevalence of obesity in 80 to 90% of Beumont's ('008) insulin-requiring diabetic subjects administered with calcitonin, is necessarily present in the method thing described by Beumont *et al.* ('008). The method of Beumont *et al.* ('008) clearly anticipates the claimed method of the instant invention, because Beumont *et al.* ('008) taught the very step of the instantly claimed method in the very same diabetic human patient. The alleged failure of Beumont *et al.* ('008) to expressly mention treatment of obesity as a goal is irrelevant. To the extent the method embodiment in the claimed invention achieves treatment of obesity, so does the method of Beumont *et al.* ('008). Where the result is a necessary consequence of what was deliberately intended, it is of no import that the article's authors did not appreciate the results. See *Mehl/Biophile International Corp. v. Milgraum*, U.S. Court of Appeals Federal Court, 52 USPQ2d 1303 and 1306, 192 F3d 1362, 1999 citing *W.L. Gore & Assocs. v. Garlack, Inc.*, 721 F.2d 1540, 1548, 220 USPQ 303, 309 (Fed. Cir. 1983).

For the reasons delineated above, the rejection should be sustained.

(VIII) In response to the rejection of claims 7, 14, 16 and 17 made in paragraph 35 of the Office Action mailed 02/11/08 and maintained in paragraph 17 of the Office Action mailed 04/30/08 under 35 U.S.C § 102(e)(2) over Gaeta *et al.* ('411) as evidenced by Tsanev, Appellants reiterate the same arguments that they have presented on the obviousness double patenting rejection over US patent 5,686,411. Appellants are referred to section V above for the Office's response.

To serve as an anticipation when the reference is silent about the asserted inherent characteristic, such gap in the reference may be filled with recourse to extrinsic evidence. Such evidence must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill.' *Continental Can Co. USA v. Monsanto Co.*, 948 F.2d 1264, 1268, 20 USPQ2d 1746, 1749 (Fed. Cir. 1991). Note that as long as there is evidence of record establishing inherency, failure of those skilled in the art to contemporaneously recognize an inherent property, function or ingredient of a prior art reference does not preclude a finding of anticipation. *Atlas Powder Co. v. IRECO Inc.*, 190 F.3d 1342, 1349, 51 USPQ2d 1943, 1948 (Fed. Cir. 1999). See MPEP 2124. Tsanev's extrinsic evidence makes clear that the missing descriptive matter, i.e., prevalence of obesity in at least one of Gaeta's ('411) insulin-requiring diabetic subjects administered with ^{25,28,29}Pro-human amylin, is necessarily present in the thing described by Gaeta *et al.* ('411). The method of Gaeta *et al.* ('411) clearly anticipates the claimed method of the instant invention, because Gaeta *et al.* ('411) taught the very step of the instantly claimed method in the very same diabetic human patient species. The alleged failure of Gaeta *et al.* ('411) to expressly mention treatment of obesity as a goal is irrelevant. To the extent the method embodiment in the claimed invention achieves treatment of obesity, so does the method of Gaeta *et al.* ('411). Where the result is a necessary consequence of what was deliberately intended, it is of no import that the article's authors did not appreciate the results. See *Mehl/Biophile International Corp. v. Milgram*, U.S. Court of Appeals Federal Court, 52 USPQ2d 1303 and 1306, 192 F3d 1362, 1999 citing *W.L. Gore & Assocs. v. Garlack, Inc.*, 721 F.2d 1540, 1548, 220 USPQ 303, 309 (Fed. Cir. 1983).

For the detailed reasons delineated above, the rejections of record should be sustained.

(11) Related Proceedings Appendix

No decision rendered by a court or the Board is identified by the Examiner in the Related Appeals and Interferences section of this examiner's answer.

Respectfully submitted,

/S. Devi/
S. Devi, Ph.D.
Primary Examiner
AU 1645

SPE Robert Mondesi
Conferee 1
AU 1645
/Robert B Mondesi/
Supervisory Patent Examiner, Art Unit 1645

SPE Jeffrey Stucker
Conferee 2
AU 1649
/Jeffrey Stucker/
Supervisory Patent Examiner, Art Unit 1649

Mr. Steven C. Koerber
Amylin Pharmaceuticals, Inc.
9360 Towne Centre Drive
SAN DIEGO, California 92121